Brain

A Journal of Neurology

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March, 1941.

BRAIN

VOL. 64, PART 1.

THE PHENOMENON OF MYOTONIA.[1]

BY D. DENNY-BROWN AND S. NEVIN.

(*From the National Hospital, Queen Square, London.*)

The condition called myotonia presents not only the subjective disability of limitation of movement, described in detail by Thomsen and others, but also the objective phenomenon of prolonged contraction resulting from mechanical or electrical stimulation of muscles as described first by Erb (1886). It has been natural to relate the persistence of willed muscular contraction, which forms the patient's disability, to the abnormality of muscular contraction produced mechanically or electrically. The basic alteration which produces the delay in relaxation of a muscle has been supposed by some to lie in the muscle itself, by others to be related to a central nervous abnormality.

The first proof of the presence of delay in relaxation in a purely "nerve-muscle preparation" was made by Grund (1919, p. 109) who demonstrated myotonic delay in relaxation of the muscle of a limb paralysed by intrathecal stovaine, and by Schäffer (1921) in limb muscle infiltrated with novocain and the motor nerve similarly blocked. Absence of action currents during the myotonic delay led Schäffer (1921) and Adie and Greenfield (1923) to believe that no central nervous discharge was concerned in the delayed relaxation. The string-galvanometer as used by them was, however, an insensitive instrument, though in the paper of the latter authors it is reported that some action currents persisted for one second, the myotonia persisting ten seconds. Gregor and Schilder (1913), and later Lindsley and Curnan (1936) with more sensitive technique, showed that

[1] This investigation was carried out in the National Hospital in 1934-35 while both authors held Halley Stewart Scholarships in the research unit. The findings were communicated to a meeting of the British Association of Neurologists at Bath in April, 1935, by one of us.—(D. D-B.)

action currents can be demonstrated in the relaxation period, and concluded that the myotonia was due to a central nervous discharge. The publication of the work of Lindsley and Curnan (1936) which had been done concurrently with our own, anticipated our main conclusion, and though we did not entirely agree with them, and had confirmed Schäffer's (1921) observation that there was a primary peripheral muscular factor, we withheld publication. The recent investigation of a family of myotonic goats by Brown and Harvey (1939) reported in a previous number of this Journal describes myotonia following percussion of denervated muscle, and has focused attention anew on the muscular factor of the disease. These authors state that the resemblance between the long persisting contraction observed by them following stimulation of a goat nerve muscle preparation and the rigidity following a sudden voluntary effort in the myotonic patient " is sufficiently obvious and needs no further comment." We have for long thought otherwise, and wish therefore to bring forward our additional evidence that myotonia as seen clinically in man has a much more complicated mechanism than the conclusions of these and other workers would appear to indicate.

Method.—The electromyogram was recorded by means of a concentric needle electrode inserted into the muscle substance, connected to a condenser-coupled amplifier and a Matthews' oscillograph recording on bromide paper strip, in the manner described previously for other work (Denny-Brown and Pennybacker, 1938). A qualitative record of the mechanical contraction was recorded on the same moving bromide paper by means of air-balloon fastened against the belly or tendon of the muscle concerned, and connected by pressure tubing to a mirror manometer. Small metal guards covering the balloon were bound on to the limb by adhesive strapping, with due care to avoid pull on the balloon by displacement of the strapping through the contraction of other muscles. With such method the magnification of the direct pressure on the balloon is such that contraction of the muscle concerned gives a pronounced deflection, contraction of other muscles a slight and negligible deflection. Careful visual control is necessary to make sure that the mechanical effect is accurately recorded.

The bellies of the muscles investigated were identified by palpation during contraction. All the patients investigated had little subcutaneous tissue and identification was thus not difficult except in the case of the deep-lying flexor profundus digitorum, for which we frequently had to search with the needle electrode, using a willed movement of the terminal phalanx and resulting action current stream to identify it.

The signal for commencement and cessation of willed movement was made with the order " grasp " and " let go " (an appropriate order for other movements). The sequel is therefore not a true index of any latency.

For recording grasping of the fingers a rubber sponge with an air-balloon inside, connected to a separate manometer, was used. This indicator gives some indication of the intensity of grasp and controls its duration, but does not record the later movements of relaxation of the fingers, and therefore does not usually show the myotonic delay which affects chiefly the later phases of relaxation.

The cases investigated included one case of congenital myotonia, one case of myotonia appearing late in life, and four cases of dystrophia myotonica.

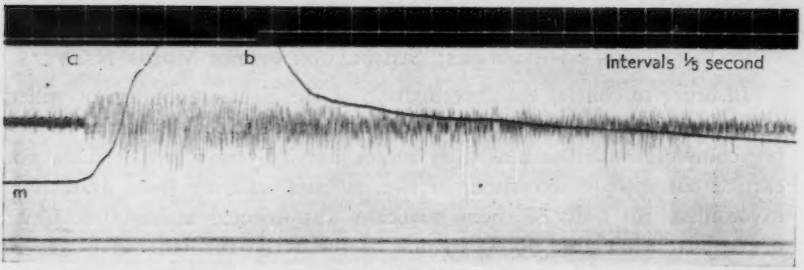

FIG. 1.—Patient M. Early dystrophia myotonica. Electromyogram of adductor obliquus pollicis. The swelling of the belly of the muscle during contraction is shown in the line *m* which records the pressure in a balloon fastened over the muscle. The patient makes a grasp from *a* to *b*, and then attempts to relax the hand. The contraction continued for 34 seconds after the end of the figure. Time shown in broad white vertical strokes at top of figure at 1/5 sec. intervals.

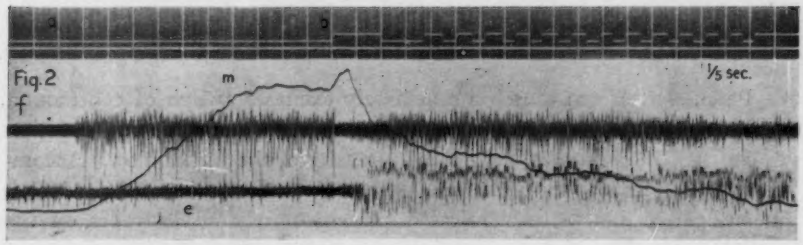

FIG. 2.—Patient MacD. Dystrophia myotonica. Two oscillographs. The upper electromyogram *f* is from electrodes in flexor profundus digitorum, the lower *e* from electrodes in extensor communis digitorum. The linear tracing *m* shows the contraction in the first dorsal interosseus muscle in the hand, recorded by balloon over it. The patient is instructed to grasp at the left of the figure, and to "straighten the fingers" at *b*. Time in vertical strokes at 1/5 sec. intervals.

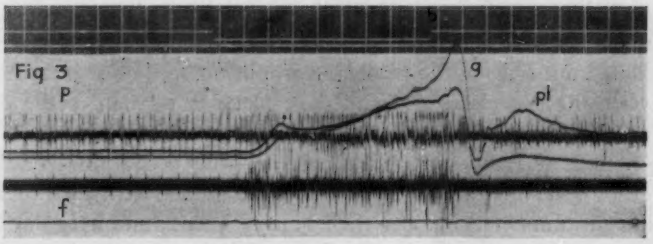

FIG. 3.—Normal subject. Two oscillographs. The upper electromyogram *p* is from electrodes in palmaris longus, the lower *f* from flexor profundus digitorum. The linear tracing *g* shows pressure in a balloon in a sponge held in the hand and tracing *pl* shows tightening of the tendon of palmaris longus at the wrist. At *a* the subject is instructed to grasp, and at *b* to attempt to straighten the fingers. The fingers are prevented from extending beyond half-flexion by adhesive strapping.

I.—The Delay in Relaxation from Contraction Artificially Stimulated by Percussion or Electrical Stimulation of the Motor Nerve.

In order to control the investigation of the electromyogram of willed movement we made records of the contraction of selected muscles following complete anæsthesia of their motor nerve by novocain. This was carried out with their consent in two patients suffering from dystrophia myotonica. In both of them novocain was injected around one ulnar nerve just below the elbow, in one of them the median nerve was in addition subjected to local anæsthesia in the same manner just above the wrist. It may be noted here that not for a long time after sensation has been lost in the appropriate skin area from such an injection is the nerve completely blocked for motor impulses, as judged by the failure of isolated muscular action currents accompanying willed effort.

Stimulation of the muscle was then made, either by percussion (direct tap on the muscle belly) or by a shock or series of shocks from a faradic coil applied to the motor nerve (ulnar in forearm), by cored hypodermic needle electrode.

Percussion of the muscle immediately excites a twitch of contraction which relaxes very slowly in the course of several seconds. The duration of contraction is proportional to the intensity of the initial blow. Accompanying the initial jerk of contraction is a large deflection of the galvanometer, partly due to mechanical displacement of the electrodes on the muscle. The long delay in relaxation is accompanied by a confusion of very small action currents, which gradually dwindle in numbers as the contraction subsides (fig. 4).

The rapid fine fluctuation of the electromyogram gives it a "fluffed" appearance, lacking the regular diphasic large deflections observable in action currents of willed or reflex movement. As the sensitivity of our recording system has been the same throughout, direct comparison may be made between fig. 4 and fig. 3. The size of the muscular action current is related not only to the recording amplification, but also to the distance between the two electrodes, and their plane in relation to the disposition of muscle fibres. Those recorded from mechanically induced myotonia are notable not only for their smallness (thus accounting for the failure of other observers to note them in human muscle with such means as the string galvanometer) but also their high frequency and irregularity. When the myotonia at last wanes after five to ten seconds it is also observed that the individual deflections are each very brief spikes.

The small rapid frequent action currents following percussion myotonia are exactly similar to those of muscle in fibrillation following denervation

which, as we have deduced elsewhere, appear to be due to waves of contraction in single muscle fibres (Denny-Brown and Pennybacker, 1938). The effect must be direct on the muscle fibre, and not on the nerve ending where any impulse set up would spread to many fibres at once and cause a regular series of large action currents. It follows that mechanically induced myotonia has the appearance of an intense independent rhythmical stimulation of each muscle fibre, this resembling the lesser spasms of muscle excited by direct injection of acetylcholine.

A single electrical shock to the motor nerve produces a small twitch without any notable delay in relaxation observable with our relatively coarse method. A few shocks in rapid succession produce a contraction followed by only slight delay in relaxation, a longer tetanic series is followed by more myotonia (figs. 5 and 6). A tetanic stimulation at 70 shocks a second for two seconds is followed by slower relaxation than that for one second. Stimulation for three seconds is longer than that after two seconds, taking eleven seconds to reach full relaxation. Continuous stimulation for nine seconds did not set up tetanic delay in relaxation (fatigue). Stimulation of the nerve at the rate of eight shocks a second just set up slight myotonia after about sixteen shocks.

It will be observed that the same "fluffed" fine rapid fluctuation of the electromyogram accompanies the myotonic delay in relaxation as accompanied the mechanical myotonia described above. The delay in its appearance after the end of the stimulus is due to the overcharging of the amplifier by the stimulus (seen in the general displacement of the galvanometer base line).

Owing to the distortion of the electrical record by the stimulating current used in this way in the intact limb we were unable to make any reliable observations on the action current of one single break-shock.

The electromyogram of the myotonic delay in relaxation of muscle thus temporarily cut off from the central nervous system has therefore a very characteristic appearance. Its "fluffiness" is on inspection found to be due to the presence of fine irregular fluctuations at high frequency (150 a second and more). In relation to the occurrence of the same phenomenon encountered in true muscular fibrillation we have elsewhere argued that this type of electromyogram represents the cumulative effect of excitation of the action current mechanism of hundreds of individual muscle fibres, each independently undergoing some form of repetitive stimulation. Excitation distributed by nerve fibres would differ in involving regularly an identical group of muscle fibres, with repetition of correspondingly larger action current of identical shape.

It will also be observed that the myotonic delay affects the latter half of relaxation much more than the earlier. We have never observed an *increase* of contraction following the stimulus, and the action currents are constantly much smaller than those of the ones induced by the stimulus. These considerations have importance compared with the phenomena consequent upon willed movement in the same muscles.

We thus confirm the finding of Grund (1919) and Schäffer (1921) that myotonic delay in relaxation from stimulation is found after regional block of the motor nerve, and find a peculiar kind of action current activity associated with the condition. The action currents in our records are much finer and more frequent than those recently recorded by Brown and Harvey (1939) in the nerve muscle preparation of myotonic goats. The other features of the discharge, however, are almost identical and we presume that the difference in size and frequency is due to our having sampled a much greater number of fibres with a somewhat less sensitive amplifying system. The closer approximation in size of myotonic action currents to those of excitation over the motor nerve in the records of Brown and Harvey (1929) is attributed by us to the same reason ; that the more localized sensitivity of their system did not allow the sampling of whole motor units, but only a few fibres at once.

Prolonged contractions of a purely neuromuscular mechanism were for long described as "contracture." Some have been shown to be associated with the presence of repetitive action currents, inducing repetitive excitation of muscle fibres, including the classical " contracture " induced by the action of Veratrin (cf. Bacq and Brown, 1937) and by acetylcholine in some concentrations (Brown, 1937). Gasser (1930) and Brown (1937) have proposed to restrict the term contracture to contractions lacking those rapid action current oscillations, such as that demonstrated by Brown (1937) following a large dosage of acetylcholine. In this sense peripheral myotonia is not then a contracture, which thereby becomes a very limited term. As we wish to describe another variety of myotonic muscular spasm, we shall term the purely muscular delayed relaxation " *peripheral myotonia.*"

Bremer (1932) has approached the problem of myotonia from the point of view of the electrical excitability of the mechanism underlying the phenomenon. He finds that it, and the similar slow relaxations, "galvanic contracture " and " neuromuscular contracture " of frogs' muscle, have a chronaxie different from a simple twitch excitation. We have no observations on this point and are unable to discuss the electrical excitabilities of the mechanisms concerned. Our electrical recording systems would

not show slow monophasic potentials. On the ground that the slow relaxation with which we are concerned is associated with rapid diphasic waves, we prefer to regard the essential mechanism underlying the maintained contraction, as that underlying normal twitch contraction. In our view, and in agreement with Brown and Harvey (1939), the phenomenon involves the excitatory mechanism of the muscle fibre (? sarcolemma) in such a way that one initial excitation causes repetitive discharge of action currents.

We have observed, as have Brown and Harvey (1939) that spontaneous bursts of action currents, each with an apparent single focus, occur in series from time to time (figs. 8 and 14). These often reach high frequencies (80 a second) for as long as two seconds. We were unable to exclude mechanical irritation of the muscle by the needle electrode as the probable initial exciting cause. Their close resemblance to the spontaneous bursts of activity found in muscle prepared with hypertonic sodium salts by Adrian and Gelfan (1933) leads us to suspect disturbances of the Na : K ionic ratio to have a close relationship to their essential cause. Brown and Harvey have shown that the muscle of the myotonic goat is abnormally sensitive to increase of potassium and to mechanical irritation.

We have observed the intense fascicular twitching induced in myotonic muscle in man following injection of *prostigmin*, and this appears to indicate an increased sensitivity of the nerve-end plate mechanism as well as of muscle fibre. The fasciculation does not in any way affect the myotonia to percussion, or the "after-spasm" we are about to describe.

II.—The Delay in Relaxation of a Willed Movement.

Clinical observation of the muscles of the forearm during and after a strong grasp in a subject suffering from myotonic persistence of grasping movement revealed to us a curious phenomenon. During the period of powerful grasp the bellies of the long flexors of the fingers and a few extensors of the wrist harden as in the normal subject, most other muscles remaining soft or only slightly contracted. Immediately the patient attempts to relax the grasp it appears that *all* the muscles of the forearm fall into spasm, their bellies rising into firm masses, their tendons standing taut. It is immediately apparent that this after-contraction involves muscles that were not previously contracting.

This spasm is particularly noticeable in the tendon of the small palmaris longus muscle, usually readily identified on the palmar surface of the wrist. Usually lying slack in the grasp, it suddenly stands taut immediately the subject attempts to relax the grasp, and remains so until the fingers have fully extended.

It is the difficulty in overcoming this spasm which forms the disability of which the patient primarily complains. It is in strong contrast with the ease with which the patient can overcome myotonic contraction evoked by percussion.

Electromyographic records were made of the contraction of the long flexor muscles during and after the grasp. During a grasping movement the action currents (figs. 9, 10, 15, 23) are identical with those of a normal subject. There is no abnormality of rhythm or size of action current. Immediately the order "relax the grasp" is given the character of the action current record changes. The action currents increase in frequency, and usually also in size (figs. 9, 15, 23). The belly of the muscle shows a very slow relaxation (fig. 9), sometimes even an increase in contraction (as in fig. 16 at *mf*). A balloon in the palm does not show the delay (figs. 11 and 23) for the initial extension of the terminal phalanges is rapid and causes a sharp fall in pressure. During relaxation there is therefore an intensification of electrical activity in the long flexors, often separated from the main contraction by a gap of 1/25 to 2/5 seconds (figs. 2, 9, 23) of relative inactivity. The electrical disturbance lasts as long as the delay in relaxation. The myotonia in our records is most commonly of this type and we find, not only the presence of action currents with myotonic delay in relaxation noted by Gregor and Schilder (1913) and by Lindsley and Curnan (1936) but an actual *intensification* of discharge in this period. This is true not only of flexor profundus, but also of the flexor sublimis. It is present in exactly the same form both in dystrophia myotonica (figs. 15 and 23) and in myotonia congenita (Thomsen's disease) (fig. 9) and in acquired myotonia (probably atypical dystrophia myotonica) (fig. 11). The additional contraction when the effort to relax is made can be observed clinically as a sudden further swelling of the muscle belly.

In muscles other than the prime mover the myotonic after-contraction was even more prominent than in the prime mover. Both in sudden increase in bulk of muscle and in size and intensity of action currents the after-contraction here often overshadowed the willed contraction which preceded it.

In the small flexor palmaris longus muscle, previously referred to, our clinical observation was confirmed. The myotonic after-contraction could here occur with all its intensity of action current rhythm when there had been no contraction *during* the period of willed grasp (fig. 17).

It was apparent therefore that the phenomenon which had attracted our attention was more than an abnormal persistence of contraction in a muscle fibre already activated. It was a sudden prolonged fresh contrac-

tion released by the patient's effort to relax, and often with a delay in onset quite unlike "peripheral myotonia." We propose to call this phenomenon "after-spasm."

It is possible that the change in intention on the part of the patient might cause him to employ his muscles in a different way in attempting to overcome a resistance to extension. An impediment in the slackening of the flexors might bring over-innervation, not only of the extensors, but also of certain muscles accessory to extension of the fingers and wrist.

Several considerations raise difficulty for this explanation of after-spasm in the myotonic grasp. The phenomenon occurs in true flexors, antagonists to extension. The action-currents are often more intense than could be produced in these same muscles by persuasion of the patient to contract them primarily. The action-current rhythm suggests a higher rate of discharge than normally occurs in willed movement, however intense. It occurred when the patient simply relaxed and made no effort to extend the fingers. Once precipitated it often could not be immediately relaxed by willed effort to renew the grasp, and could develop into a generalized spasm of the whole limb. The phenomenon is readily fatigued and recovers after rest, a well-known feature of the myotonic grasp. The muscles concerned are those which oppose the intended relaxation of grasp, whereas the electromyogram of the extensors of fingers and wrist at the same period shows a regular but intense discharge of the normal action current waves of willed movement (fig. 2). Experiment showed that palmaris longus contracts very slightly in extension of the wrist or fingers in the normal subject (fig. 3) in the strongest effort, even against resistance. Lastly, the phenomenon, though generalized in myotonia congenita, is usually very localized in dystrophia myotonica, just as peripheral myotonia to percussion is more localized in the early stages of the latter syndrome. Hence after-spasm was found in flexor carpi ulnaris *only when the primary movement was a grasp* (fig. 22), and not at all when the primary movement was ulnar deviation of the wrist (fig. 21).

Thus the phenomenon of after-intensification of contraction and electromyogram in dystrophia myotonica appears to be an involuntary spasm of both prime movers and synergists for *the movement of grasp.* It can occur in less degree in extensors of the fingers when that is the prime movement, and can occur in minor degree in either set of opposing adductors and abductors of thumb (figs. 1 and 24). Brief outbursts at high frequency, such as are seen in the abductor at the onset of adduction (fig. 24) may be due to movement of the needle among the muscle fibres. The general characteristics of "after-spasm" cannot have explanation in this way.

Close inspection of the action currents of "after-spasm" of muscles following willed movement reveals that it is made up of repetitive series of large action currents, each in a series being of identical shape (cf. figs. 2 and 13). When the discharge in general is not too intense the rhythm is from 7 to 20 a second, so that the eventual decline of the contraction often resolves into the electromyogram characteristic of postural central nervous discharge. As the discharge lessens a renewal of willed grasping contraction sometimes brings about abrupt cessation of these large action currents, before the fresh contraction commences (fig. 18). Thus it appears that it is possible for these large action currents to be inhibited centrally, a feature that, in addition to their large size and regular rhythm, identifies them positively with discharge of motoneurones.

Frequent repetition of the primary movement (e.g. grasping) results at first in intensification of the spasm and accompanying action currents, and the electromyogram of each successive grasp appears more intense and of greater frequency. This is particularly marked in myotonia not accompanied by muscular atrophy, where a spasm lasting one or two minutes may sometimes be set up, associated throughout with the type of discharge shown in figs. 7 and 11. More often the spasm lessens and disappears with six to ten repetitions of the grasp, then showing a few action-current rhythms of regularity and size corresponding to motoneurone discharge (fig. 20).

For the elicitation of the spasm of clinical myotonia following willed movement described above the patient is caused to make a powerful grasp (cf. figs. 10 and 11). The particular virtue of intensity of contraction in eliciting myotonia is a common clinical observation and this applies to whatever group of muscles is examined (e.g. orbicularis oculi).

III.—True Peripheral Myotonia from Willed Movement.

We have observed earlier that percussion myotonia and the delay in relaxation following stimulation of the peripheral nerve (electrical myotonia) have a peculiar "fluffed" electromyogram due to the presence of many small action currents. This type of electromyogram is also seen following voluntary contraction. In records of more gentle grasp movement it will be seen (fig. 10) that the very distinctive after-discharge of spasm is lacking. The patient no longer complains of spasm, no longer feels an effort to relax the fingers, though a delay of smaller kind may still be obvious in the record of mechanical relaxation. The electromyogram is not entirely quiescent, and shows a vibratory oscillation of high frequency and small amplitude identical with that described above and pictured

accompanying myotonia following mechanical percussion of the muscle and electrical stimulation of the nerve (cf. figs. 4 and 5). This type of electromyogram of relaxation is also seen when repeated contraction and relaxation has fatigued the myotonic delay in grasping (fig. 19). The large action currents are less and less evident in successive relaxations. The fingers then relax rapidly to full extension though the bellies of the prime movers still relax slowly and a "fluffed" electromyogram is seen.

In the small muscles of the hand this type of after-contraction is most usually obtained and few large action currents complicate the picture. Fig. 1 is characteristic of a fresh contraction in adductor obliquus pollicis in a dystrophic patient. Few sparse large action currents are seen, although the delay in relaxation is remarkable. It will be noted that the small action currents follow directly upon the action currents of the voluntary movement. In less intense movements the "fluffing" can be seen to develop during the later stages of the movement. Pure "peripheral" myotonia is therefore present here. In extreme fatigue it too disappears leaving a completely quiescent relaxation.

In some muscles this "fluffy" discharge can be seen in the gaps between the larger action currents late in the willed movement (figs. 10, 15 and 20), in the gap before spasm occurs (figs. 2 and 23) and in the gap between partial inhibition of spasm and onset of further willed movement when that is possible (fig. 18).

We have observed that in dystrophia myotonica the myotonia following percussion of the same muscles is fatigued later than myotonic "spasm" by repetition of the same movement. In pure myotonia it appears often possible to fatigue the liability to spasm and still be able to elicit myotonia by percussion.

We conclude therefore that the muscular spasm which is associated with real difficulty in relaxing a willed grasping or other movement in association with myotonia is due to discharge of central motoneurones, and is distinct from, although intimately associated with, the purely muscular phenomenon of delayed relaxation in the same or related myotonic muscles.

At this stage it is convenient to set out the chief distinctions between the two types of myotonic phenomenon:—

After-spasm (Central).	*Muscular Myotonia* (Peripheral).
(1) Large action currents.	(1) Very small action currents.
(2) Increase of intensity compared with the preceding contraction.	(2) Only a small percentage of the preceding contraction.
(3) Easily fatigued.	(3) Difficult to fatigue.

After-spasm (Central).	*Muscular Myotonia* (Peripheral).
(4) Not necessarily related to previous contraction in the same muscle.	(4) Determined by and proportional to the intensity of previous contraction in the same muscle.
(5) Not elicited by percussion.	(5) Elicited by percussion.
(6) Onset delayed by as much as 2/5 second when in weak or moderate degree.	(6) Is maximal immediately the eliciting contraction ceases and thereafter wanes.
(7) Impedes the action of opposing muscles.	(7) Very weak opposition to opposing muscles.
(8) In early dystrophia myotonica may appear in fixators of wrist only when synergic with grasp movement and not when used as prime mover.	(8) In early dystrophia myotonica may be elicited only in the small muscles of the hand, and in the tongue.

The Origin of the Central Discharge following Strong Willed Movement.

The recorded pathological findings in the nervous system of patients suffering from dystrophia myotonica are not such as to account for the persistent central discharge in terms of disorder of the structures known to regulate tonic reflexes. The known abnormality in structure and contraction of the muscle fibres is the only constant pathology of the disease (*see* Adie and Greenfield, 1923). There is much to support the view that the process responsible for the phenomenon of myotonia is the same in both dystrophia myotonica and in myotonia congenita. Maas and Paterson (1939) have recently adduced evidence towards the recognition of both syndromes as one and the same disease. Though we prefer the older clinical distinction, and have not seen transitions from one to other, our patient N. (figs. 10 to 14) in whom generalized myotonia was associated with general hypertrophy of musculature, especially that of the forearms and hands, had early opacities in the lenses of both eyes. We would regard this condition as a variant of dystrophia myotonica. Several such cases have been described in the literature (Adie and Greenfield, 1923).

Experience with various stages of the evolution of the disease dystrophia myotonica leads us to the conclusion that the objective signs following direct percussion of the muscle may long precede any subjective sensations of delay in willed relaxation and we agree fully with Adie and Greenfield (1923) who state " many patients in whom myotonia can be demonstrated objectively have never had subjective symptoms." Indeed it would appear that the disease can sometimes progress to atrophy without the patients ever suffering disability in relaxation of willed movement. We find in our records no essential difference in the myotonic phenomena

in the two states acquired myotonia and dystrophia myotonica except the distal onset and incidence in the musculature of the latter disease. There is no electromyographic difference between records from congenital myotonia (fig. 9), acquired myotonia (fig. 11) and dystrophia myotonica (fig. 23).

In dystrophia myotonica it is not uncommon to find marked myotonic delay in relaxation of willed movement in the upper limb related solely to movements of the hand, especially the grasp. In such a patient, having recorded the electromyogram of the muscles of forearm and hand, the long flexors showing the characteristic burst of activity with attempt to relax, we proceeded to block the ulnar nerve just above the elbow, with novocain, and the median nerve also just above the wrist. Complete anæsthesia in the appropriate areas, and complete lack of willed ability to throw the intrinsic muscles of the hand into contraction ensued. These intrinsic muscles showed the myotonia from percussion and electrical stimulation of the nerves. Yet it was most remarkable that now the patient was able to make and relax his strongest grasp (by contraction of long flexors) without delay. This effect did not appear to be due to the circulation of novocain directly to the flexor muscles for they were far from the site of injection. If novocain were present in the circulation it had not affected the phenomenon in the other hand. After recovering from the anæsthesia of the median and ulnar nerves the myotonic delay in relaxing the grasp affected the forearm as before.

In this experiment, therefore, we found suggestive evidence that the spasm accounting for delay of relaxation of willed grasp, though due to nervous discharge, is determined primarily by the myotonic condition of the small intrinsic muscles of the hand. The essential myotonia of these muscle fibres determines the central discharge. In another patient it was observed that fatigue of "after-spasm" in the whole forearm resulting from forceful flexion of one finger did not prevent renewal of the spasm following a forceful flexion of another finger. Again a peripheral source for the widespread spasm was indicated. The nervous discharge underlying the spasm following willed grasp might, for instance, be reflexly determined by some persistent effect in the proprioceptors of these intrinsic muscles, acting reflexly.

The "positive supporting reaction" of Magnus is such a reflex, arising in proprioceptors in the distal part of the limb and reinforcing the contraction of a synergic group of palmar flexors. The muscles synergic in the willed grasp are just such a group, and if these include fixators of elbow as well as wrist we can add that the myotonic spasm following a strong grasp also occasionally involves these elbow fixators such as biceps with the characteristic rhythm of motoneurone discharge.

The "after-spasm" following willed movement in congenital or acquired myotonia is not limited to the grasp. Here the spasm may involve a whole limb, or the whole body, resulting in the curious falls commented upon by Adie and Greenfield (1923) and others. Such a spasm appears sometimes to follow immediately upon intended movement after a period of relative relaxation. For example, our patient S. while fielding in cricket, and having been standing still for some minutes, intended suddenly to run, only to fall in a general spasm.

It has been noted by a number of observers that myotonia following stimulation of the motor nerve is the more intense the more rapidly repeated the tetanic stimulus. Motoneurone discharge is normally most rapid at the commencement of rebound from a period of inhibition, or at the onset of a phase of rapidly alternating movement, and myotonia commonly occurs at these times.

Thus, in an experiment with the short adductors and short abductors of the thumb in a myotonic patient, the abductor muscle was found to show an outburst at the commencement of adduction as well as the adductor at the beginning of abduction (fig. 24).

In muscles like palmaris longus it is not uncommon in the normal subject to find an active motoneurone discharge associated with some unwitting posture of the hand, and this discharge ceases during a grasping movement only to return immediately the movement is over. Such postural discharge can be relaxed at will. It also occurs in myotonic patients, and the return of its postural discharge following the grasp may provide a possible basis for the pathological rebound myotonic contraction. The myotonic spasm, however, occurs as before when the grasp is made in such a manner as not to disturb the posture of palmaris longus and is still just as intense in that muscle. We are therefore not inclined to explain the discharge as heightened rebound of previously existing posture, a phenomenon which has its own characteristic electromyogram of clonic outbursts in the normal electromyogram.

We have already noted the objections to regarding the "after-spasm" as simply the patient's intense effort to extend the fingers. The involvement of palmaris longus and flexor carpi ulnaris in this process may be in part due to the subject's effort to fix the wrist in half-flexion the better to extend the fingers, but the nervous spasm in the long flexors of the fingers themselves cannot be explained in this manner, particularly when these show little or no purely muscular myotonia, as in many cases of early dystrophia myotonica.

We have made an extensive investigation of the action of synergists

in normal subjects and under conditions of spasticity, rigidity, and reflex grasping, but failed to find any phenomenon comparable to the "after-spasm" of myotonia. In these either persistence of contraction or clonic rebound occur with action currents of normal frequencies. Synergism with grasp is a "dead-beat" contraction, without after-discharge, when the muscle fibre is normal.

We are forced to conclude that when myotonia occurs in muscle with its nerve supply intact the onset of the purely muscular myotonia during and following willed innervation reflexly sets up a condition closely allied to, if not identical with, common cramp in the muscles concerned. As we have previously described (Denny-Brown and Pennybacker, 1938) cramp is associated with an intense discharge of nervous type though undoubtedly of primarily muscular origin. Once set up it tends to involve the whole muscle, or muscle group, becoming a reflex spasm induced from the muscle itself and assisted in relaxation by intense innervation of antagonists. We believe that the same mechanism appears in myotonia, invoked here primarily by intense muscular activity in a few muscle fibre groups and spreading rapidly to involve other and unrelated muscular groups. Thus, if percussion myotonia be related almost solely to the small muscles of the hand the myotonic spasm may still be elicited in the forearm.

Simple muscular cramp is painful, and the usual painlessness of myotonia would appear to be a serious bar to relating the two processes. We believe, however, that the difference is one of degree rather than one of kind, and have found severe myotonic spasm to be described as painful or unpleasant. The small wavelike fluctuations of muscle called myokymia, associated with muscular cramps in some cases have been shown by spinal anæsthesia to be independent of central nervous mechanism (Grund 1919), though the intense form of cramp would appear to require a central mechanism.

Conclusion.

Our findings in myotonic muscles indicate that the mechanism of delay in relaxation of a willed muscular contraction in patients suffering from dystrophia myotonica and myotonia congenita (Thomsen's disease) is a complicated phenomenon. A willed contraction of truly myotonic muscle sets up a state of "peripheral myotonia" in that muscle. The difficulty in willed relaxation is not due directly to this peripheral myotonia but to reflex (central) spasm of the prime movers and synergists.

We consider that appreciation of this finding is essential if the phar-

macology of the disease is to be estimated soundly, for we believe the effect of fatigue, and possibly of drugs, is different on the two processes. The pharmacological aspect is too large to be pursued further here.

As far as our observations on the human "nerve-muscle preparation" are concerned we are completely in agreement with those who have for so long argued that the disease is essentially a muscular disorder. The abnormality is one of excitability of the muscle fibre, of such nature that one excitation leads to repeated discharge of the action-current mechanism of the muscle fibre. Such may well be an exaggeration of a normal feature of the mechanism of contraction recently found by Eccles and O'Connor (1938), who demonstrate subsidiary excitations in some muscle fibres in normal muscles following one nerve impulse.

Finally it may be remarked that the high frequency of reflex discharge in "after-spasm" in muscles not otherwise myotonic may be held to be accountable in part, if not wholly for the hypertrophy of muscle fibre which forms one of the histological features of the disorder. It may be noted that in Thomsen's disease and acquired myotonia where hypertrophy of muscle fibres and whole muscles forms a unique feature, widespread spasm are the rule.

Thus it appears desirable to clear away the central nervous complications of this affection in order to arrive at a proper conception of both its true mechanism and morbid histology.

The authors wish to express their indebtedness to the various members of the staff of the National Hospital who allowed access to their patients for this investigation, and to the willing co-operation of the patients concerned. The electromyographic apparatus used was provided by the Medical Research Council.

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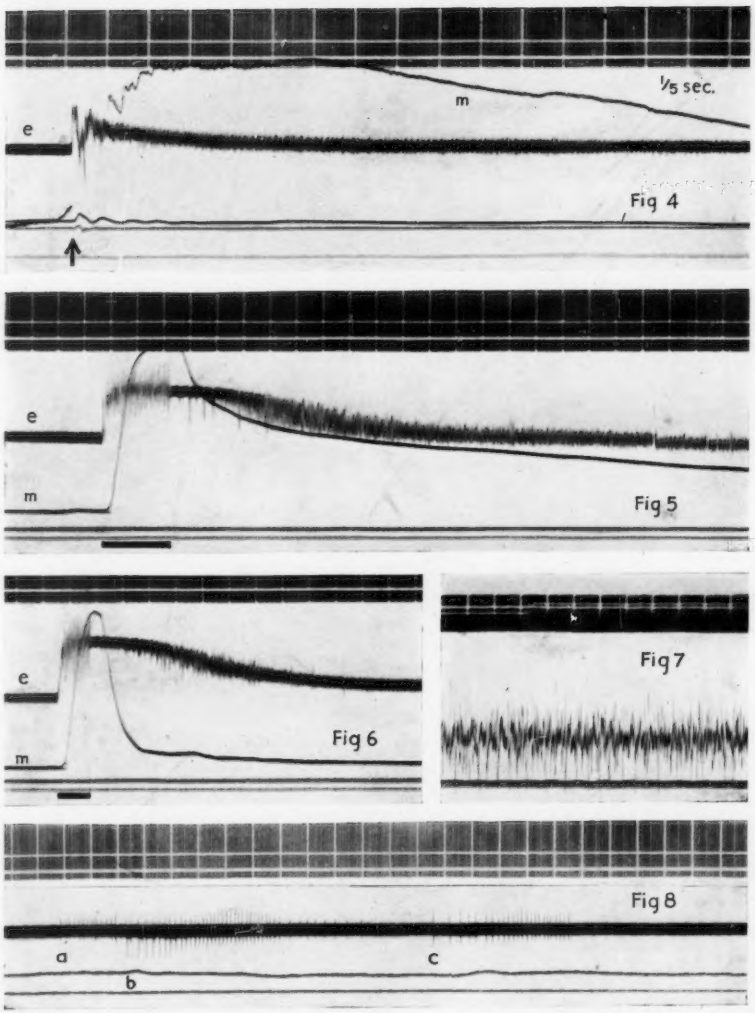
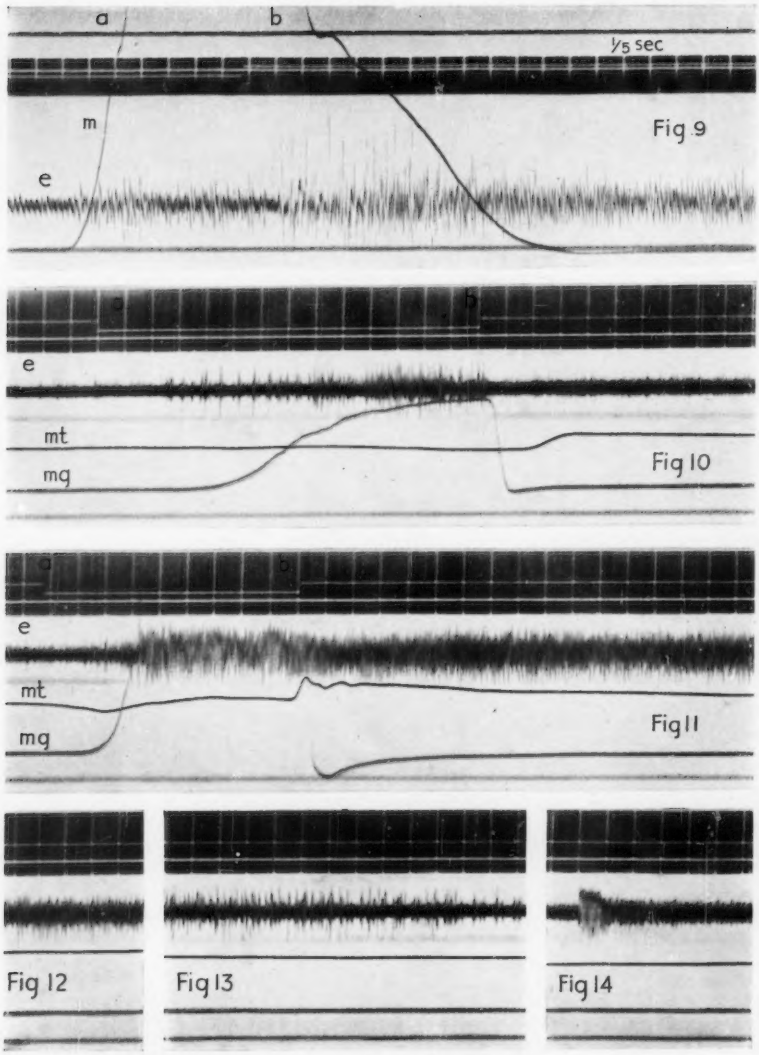
PLATE I.



To illustrate article by D. Denny-Brown and S. Nevin.

PLATE II.



To illustrate article by D. Denny-Brown and S. Nevin.

PLATE III.

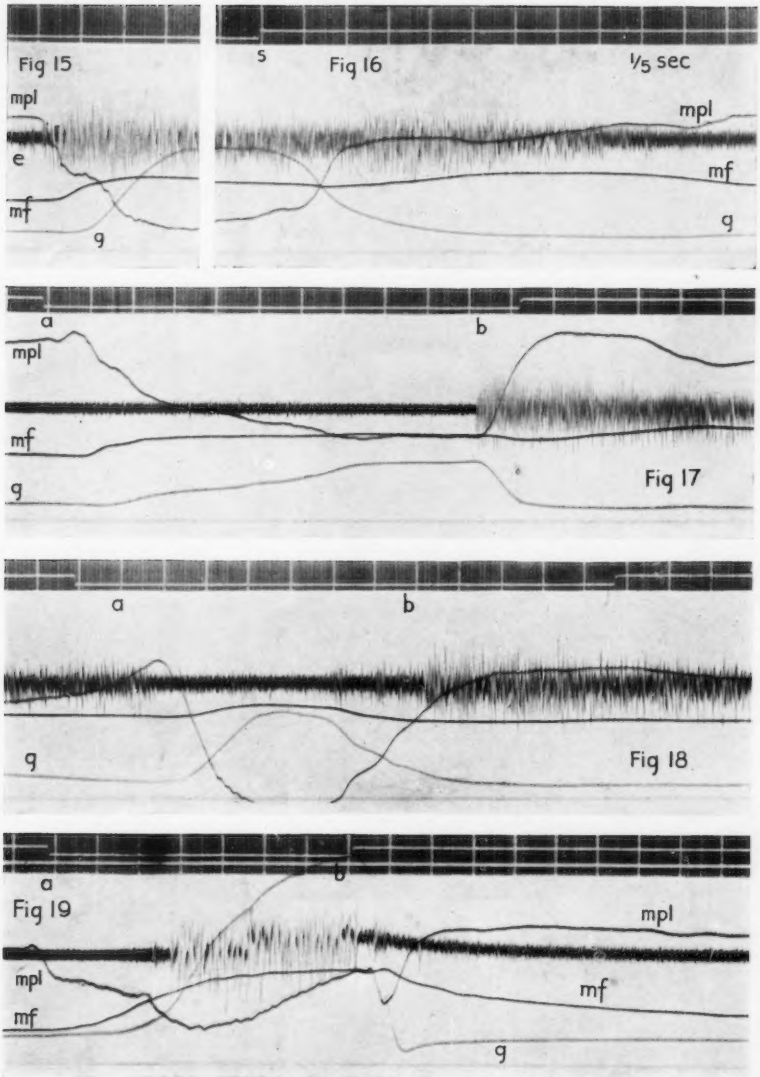


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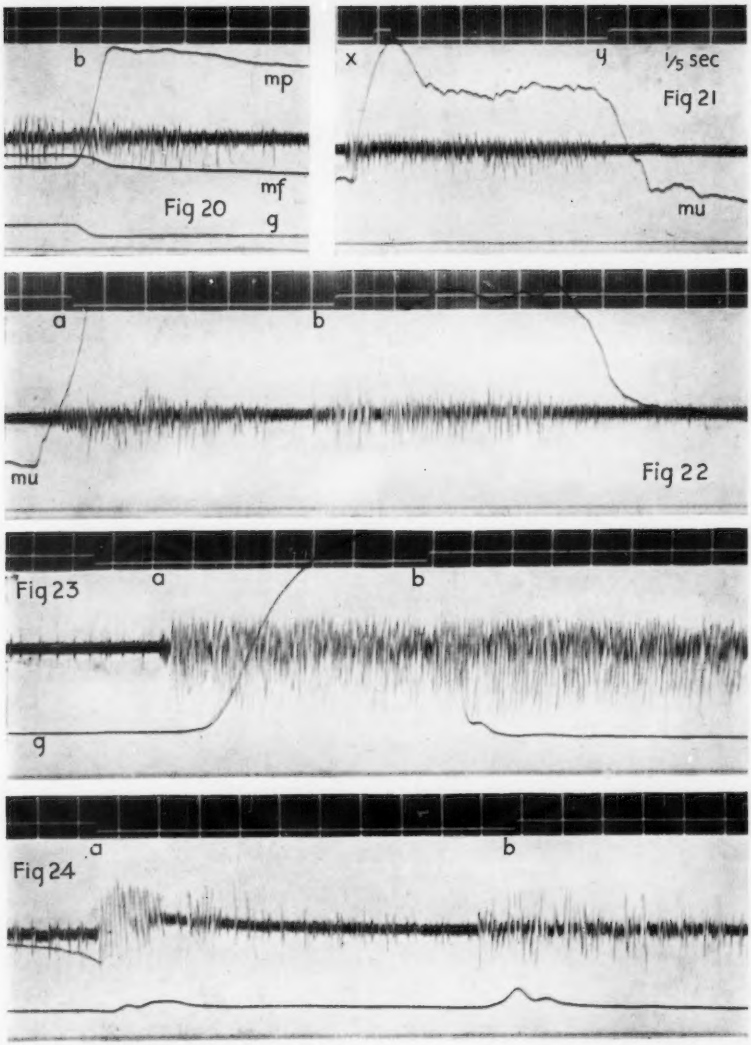
PLATE IV.



To illustrate article by D. Denny-Brown and S. Nevin.

LEGENDS FOR PLATES.

PLATE I.

FIG. 4.—Patient MacD. Dystrophia myotonica. From abductor pollicis, with record of the mechanical contraction *m*, and electromyogram *e*. The muscle is percussed briskly with a rubber-tipped hammer at the arrow. The initial vibration is due to the mechanical impact. The contraction induced slowly subsided and the first three seconds are shown here. The base line was reached sixteen seconds later. Time in all figures shown by vertical strokes at intervals of 1/5 second.

FIG. 5.—The same patient. First dorsal interosseus muscle. The contraction curve *m* is recorded by balloon over the muscle, electromyogram *e* from proximal fibres of the same muscle. The ulnar nerve has been fully anæsthetized just above the elbow by perineural instillation of novocain. Stimulating electrodes are applied to the nerve trunk at the wrist through an insulated needle. For the duration of the short black line a series of faradic make and break shocks from a coreless coil at 5 cm. is applied to the nerve below the block. The stimulus current temporarily disturbs the amplifiers, which commence to record action currents after the end of the stimulus, during the decline of the contraction.

FIG. 6.—As fig. 5, brief stimulus.

FIG. 7.—Patient S. Congenital myotonia. Action currents of flexor sublimis digitorum during a maintained spasm lasting some minutes, following several grasps of the hand in succession. The whole limb was in spasm and could not be relaxed voluntarily.

FIG. 8.—Patient S. Congenital myotonia. Bursts of action currents occurring at rest in quadriceps extensor of knee. The onset of three series is at *a*, *b*, and *c*.

PLATE II.

FIG. 9.—Patient S. Congenital myotonia. Flexor sublimis digitorum. Mechanical record *m* and electromyogram *e* during a grasp from *a* to *b* and ensuing relaxation. Time in vertical strokes at 1/5 sec. intervals.

FIG. 10.—Patient N. Acquired myotonia, with hypertrophy of muscles. Electromyogram of flexor profundus digitorum. A balloon in a sponge records the grasp contraction *mg*, and another balloon over the tendons on the anterior aspect of the wrist records their tightening *mt*. The subject grasps gently from *a* to *b*. Very slight electrical discharge continues after *b*.

FIG. 11.—Direct continuation of the record shown in fig. 10. A more powerful grasp from *a* to *b* is followed by intense discharge.

FIG. 12.—Forty seconds after fig. 11. The patient is attempting to relax.

FIG. 13.—One minute after fig. 12. The discharge is lessening.

FIG. 14.—Same patient. During a period of rest a brief spontaneous outburst at high frequency occurs in the electromyogram.

PLATE III.

FIG. 15.—Patient C. Dystrophia myotonica. Electromyogram of flexor profundus digitorum *e*. The patient is instructed to grasp just as the record begins. The lower line *g* records the pressure in a balloon embedded in a sponge held in the hand and thus shows the grasp pressure. The middle line *mf* shows the mechanical swelling of the bellies of the flexor muscles of the forearm during contraction. The upper line *mpl* shows the pressure in a small balloon over the tendon of palmaris longus which relaxes as the grasp is made. Time in 1/5 sec. intervals.

FIG. 16.—Continuation of the record of fig. 15 after an interval of 1 second. At the fall of the signal line *s* the patient is instructed to relax the grasp. A further outburst of large action currents is seen in the electromyogram.

FIG. 17.—As figs. 15 and 16, but the electromyogram is from palmaris longus. Mechanical records as fig. 15. Grasp from *a* to *b*.

FIG. 18.—As fig. 17. Electromyogram of palmaris longus. The patient is instructed to grasp from *a* to *b*, during spasm already initiated by a grasp and relaxation 4 seconds earlier. The nervous discharge is seen to lessen greatly during the renewed grasp.

FIG. 19.—Patient MacD. Dystrophia myotonica. Electromyogram of flexor profundus digitorum. The line *g* shows the pressure in a balloon in a sponge in the hand. The line *mf* shows swelling of the bellies of the long flexor muscles during contraction. The upper line *mpl* shows relaxation of the tendon of palmaris longus at the wrist. The patient is ordered to grasp at *a* and to relax at *b*. The delayed relaxation of the long flexors is accompanied by fine action currents.

The contraction here recorded is the last of a long series of grasps and relaxations, when myotonia was nearly completely fatigued, and the movement of the fingers unimpeded.

PLATE IV.

FIG. 20.—Patient C. Dystrophia myotonica. Electromyogram of flexor profundus digitorum, fatigued by repeated grasping. The lines show pressure of grasp on a balloon in the hand *g*, swelling of the bellies of the long flexors *mf*, and relaxation of the tendon of palmaris longus at the wrist *mp*, as in fig. 15 with which this should be compared. After a long grasp the patient is instructed to relax at *b*. The mixed large and small action currents during relaxation are to be noted. Time in 1/5 sec. intervals.

FIG. 21.—Patient C. Dystrophia myotonica. Electromyogram of flexor carpi ulnaris, and record of the swelling of the belly of the same muscle *mu* during and after ulnar deviation of the hand from *x* to *y*.

FIG. 22.—As fig. 21, but the patient is instructed to grasp at *a* and to relax at *b*.

FIG. 23.—Patient M. Dystrophia myotonica (Early). Electromyogram of flexor profundus digitorum. The line *g* records the pressure in a sponge in the hand during the height of the grasp, which is made at *a* and relaxed at *b*.

FIG. 24.—Patient M. Dystrophia myotonica. A few minutes after fig. 23. Electromyogram of abductor brevis of the thumb and swelling of the same muscle when a grasp is made at *a* and relaxed at *b*. Note outburst of action currents at the onset of the grasp.

VITAMINS E AND B_6 IN THE TREATMENT OF MUSCULAR DYSTROPHY AND MOTOR NEURONE DISEASE.

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In 1928 Evans and Burr showed that the suckling offspring of vitamin E deficient rats developed paralysis. Goettsch and Pappenheimer in 1931 produced muscular dystrophy in guinea-pigs and rabbits by feeding them on a deficient diet. This diet has since been shown to be deficient in vitamin E, and more recently it has been demonstrated that this nutritional muscular dystrophy could be prevented and cured by synthetic α-tocopherol. A different condition occurs in adult rats fed on a diet deficient in vitamin E. Ringsted in 1935 and Einarson and Ringsted in 1938 showed that adult rats developed paralysis associated with a pathological picture in the spinal cord resembling a combination of amyotrophic lateral sclerosis and tabes dorsalis.

Muscular weakness associated with degenerative foci in the muscles was found by Antopol and Unna (1940) to occur in rats deficient in vitamin B_6, though the main feature of the deficiency is a peculiar skin condition referred to as rat acrodynia. They further demonstrated that massive doses of synthetic vitamin B_6 produce in rats muscular tremors, convulsions, and marked impairment of righting reflexes.

As a result of these experimental findings vitamins E and B_6 were tried in human neurological disease and in 1940 both vitamins were hailed as giving satisfactory clinical results in muscular dystrophy and amyotrophic lateral sclerosis. These results have been recorded in muscular dystrophy by Bicknell (1940) and Stone (1940) using vitamin E, and by Antopol and Schotland (1940) using B_6. Improvement with vitamin E in cases of amyotrophic lateral sclerosis was noted by Bicknell (1940), Wechsler (1940 *a*, *b*), and Spies (1940). Spies, Hightower and Hubbard (1940) also found vitamin B_6 effective in this disease. Both vitamins have been claimed to be of value in a variety of other neurological conditions.

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† Work undertaken whilst holding a Research Fellowship in Diseases of Muscle of the National Hospital for Nervous Diseases.

In view of these findings a further inquiry into the treatment of muscular dystrophy and motor neurone disease with vitamins E and B_1 was considered justifiable.

Methods.

Selection of cases.—Cases as far as possible were confined to those in which the diagnosis was not in doubt, and in which the disease was not so far advanced that considerable relief could not be obtained should its natural history be altered. No effort was made to distinguish between amyotrophic lateral sclerosis and progressive muscular atrophy, as we accept the view that they represent stages in the same motor neurone disease. Nineteen cases in all have been studied; ten have been classed as motor neurone disease, and nine as cases of muscular dystrophy, five of which were of the pseudohypertrophic type, two of the Erb juvenile form, one of the Buzzard pelvic type, and one was a case of amyotonia congenita. One further case has been included, and has been classed as a muscular dystrophy, but it may have been an atypical case of motor neurone disease occurring at a very early age. It has been included because though it may not be a dystrophy but a case of motor neurone disease, nevertheless according to other workers it should respond to treatment with either vitamin.

The period under observation in hospital varied from four to eleven weeks with a mean of eight weeks, whilst the total period of observation in 19 of the cases varied between nine to thirty-seven weeks, with a mean of twenty-four weeks. In one case no follow-up was practicable after an initial period in hospital of eleven weeks.

Criteria of change.—Change in the state of the patient was observed both clinically and biochemically. Clinical change was considered under subjective and objective headings. Originally it was our intention to note objective improvement ergographically, but the method was found to be of doubtful value and was given up. Simple tests of muscle power, such as the patient's ability to lift known weights and perform simple exercises was found to give more reliable results. Control periods, using inert substances under similar guise, were instituted in a few of the small number of cases in which subjective improvement occurred. Importance was attached to this as other workers had considered that a temporary withdrawal of the vitamin resulting in a transient relapse as "a crucial physiological and clinical experiment indicating that recovery was the direct result of the treatment." Prior to treatment a control period of not less than a week under observation was instituted.

Creatine-creatinine metabolism.—On admission the patient was placed on a standard low creatine diet excluding meat and fish or their extracts. Twenty-four-hourly urines were collected and estimated daily for creatine and creatinine by the method of Folin (1914). A control period, usually a week or more, was allowed before treatment was started. The patients were weighed at weekly intervals.

Dosage.—Vitamin E has been said to consist of two or more factors. The whole complex is present in either the proprietary preparation Bemax or in wheat germ oil. Viteolin consists of tocopherol in oily solution, and one capsule contains 6 mg. of α-tocopherol, i.e. the extracted product of about 5 grm. of wheat germ oil. The synthetic d l-α-tocopherol acetate is closely related to α-tocopherol, has similar potency and has been found by Verzar (1939) and other workers to cure nutritional muscular dystrophy in rats. All these substances have been used in the treatment of our cases both alone and in combination. The dose used has been varied both in the same and in different patients. In every case, however, the dose was the same or more than that employed by previous workers with the exception of Spies and Vilter (1940) who have used 500 mg. of d l-α-tocopherol acetate in one dose given by injection. However, on the occasions that we used 300 mg. of d l-α-tocopherol acetate parenterally it was combined with 108 mg. of α-tocopherol orally and given over a period. In treating the earlier cases the usual dose administered was 18-36 mg. of α-tocopherol daily, but in the later cases this dose was far exceeded, 108 mg. being given daily, either alone or in conjunction with 300 mg. of d l-α-tocopherol acetate.

Vitamin B_6—2-methyl-3-hydroxy-4, 5-dihydroxy methyl pyridine (pyrodoxin)—has been given as a synthetic preparation. In all cases it was administered parenterally either subcutaneously, intramuscularly, or intravenously. In a number of cases it has been used in conjunction with α-tocopherol or d l-α-tocopherol acetate. It has been injected in 50 or 100 mg. doses.

Results.

Twenty cases are presented under the two main headings of motor neurone disease and muscular dystrophy. Because of the failure to note any significant improvement in either group of patients, higher doses of vitamins E and B_6 were given in the later cases. In one case of motor neurone disease injections of vitamin B_6 were combined with massive doses of vitamin E. Cases of muscular dystrophy have been subdivided into those receiving vitamin B_6 alone, those receiving α-tocopherol, those receiving both B_6 and α-tocopherol, and a single case receiving B_6 paren-

terally, α-tocopherol orally and d l-α-tocopherol acetate parenterally. These cases have been classified on the basis of their treatment whilst in hospital. Since discharge all cases have received either vitamin E, α-tocopherol or d l-α-tocopherol acetate.

For details of these cases see Appendix (1).

Of the ten cases of motor neurone disease two died while under treatment with α-tocopherol (Cases 1 and 2). In the former fibrillation of tongue commenced while on treatment in hospital with an increase in muscular weakness of a generalized character. This deterioration continued following discharge and the patient died some months later. In the second case dysphagia commenced in hospital and this patient also died following discharge.

Two further cases have since been admitted to other hospitals owing to continued deterioration (Cases 5 and 8). In Case 5 no change was noted in hospital, but some months later the condition of the patient had obviously deteriorated with increased muscular fibrillation and weakness. In the latter case (Case 8) so weak had the patient become when last seen that he had difficulty in maintaining the erect posture, and his gait was seriously impaired. Of the remaining three cases who were noted as being subjectively better on leaving hospital, one has since become considerably worse (Case 7). This patient's gait has become shuffling owing to increase in weakness of the dorsiflexors of the feet.

Cases 6 and 10 are still subjectively better, but without clinical evidence of this improvement. Case 10 received intensive therapy while in hospital, but at no stage was an increase in power noted.

In the muscular dystrophy group, four were classed as being subjectively better, but at no stage could this be demonstrated clinically. These included two cases of the Erb juvenile form (Cases 14 and 15). The former was treated with vitamin B_6 whilst in hospital, the latter with α-tocopherol. The next case (Case 17) showing subjective improvement, as already noted, gave rise to some difficulty in diagnosis and was treated with α-tocopherol. Case 19, of the Buzzard type, was treated with the vitamins E and B_6 in combination, but again without clinical evidence of improvement in the condition.

The remaining six cases, including all five of the pseudohypertrophic variety of dystrophy, whether treated with vitamin B_6 alone or in conjunction with vitamin E, showed neither subjective nor objective improvement whilst in hospital though Case 11 has since certainly become weaker and now has difficulty in walking.

Creatine-Creatinine Metabolism.

The assessment of minor changes in the state of the patient must to a large extent depend on clinical impression, and the literature on vitamins abounds in examples where this has been at fault. We have therefore attempted to control our clinical observations by estimating daily the creatine and creatinine output in the urine before and during treatment.

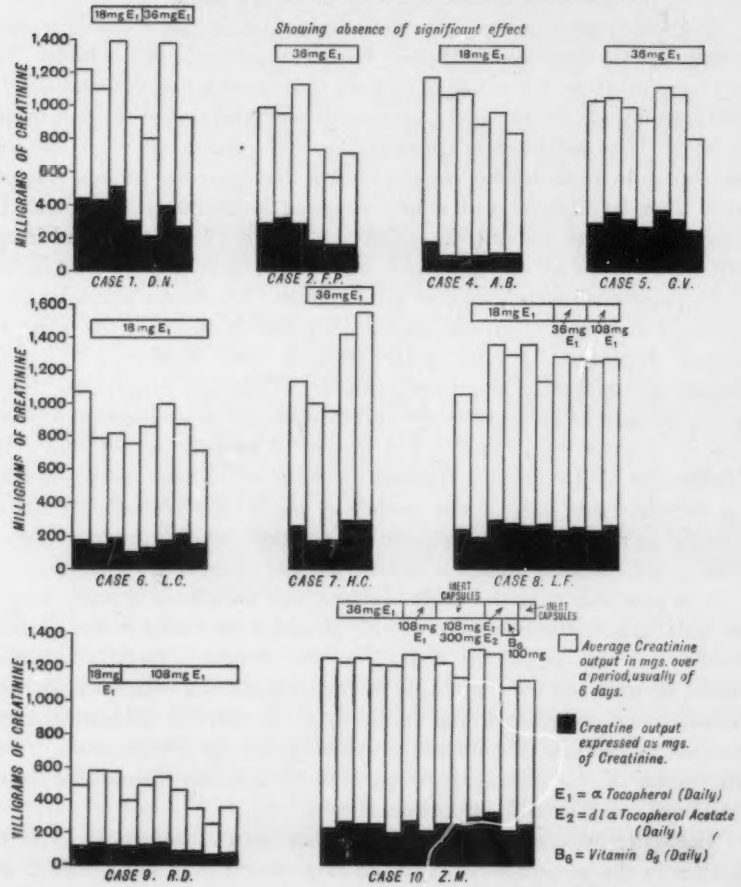
The daily output of creatinine in the urine is generally accepted as being an index of the amount of properly functioning muscle in the body. It is very constant from day to day in any one individual but varies considerably with age and sex, the variations appearing to depend on the mass of muscle present. Thus adults pass considerably more creatinine than children, and men more than women, though athletic and muscular women may pass more than an ill-developed man. Creatine is normally present in the urine in moderate amounts in childhood, and to a less extent and irregularly in the urine of women, but is not present or is present only in very small quantities in the urine of adult males. In certain conditions, but especially in disease of muscle, creatine is found in excess in the urine, the amount depending, according to Milhorat and Wolff (1937), on the amount of improperly functioning muscle. Thus in a generalized disease of muscle such as progressive muscular dystrophy more creatine is passed than in diseases where only a few groups of muscles are affected. The relationship of the urinary creatine to the mass of improperly functioning muscle holds only if the subject is on a creatine-free diet, as the capacity to store ingested creatine is dependent on the mass of efficient muscle, and diseased muscle is unable to store exogenous creatine.

It is probable that the daily creatine and creatinine urinary outputs are only approximate indices of the amounts of healthy and diseased muscle, but any significant change in the clinical state of the patient should be reflected by alterations in the creatine and creatinine outputs. Improvement therefore would result in an increase in creatinine and a decrease in creatine, the opposite occurring during deterioration. With progression of the disease there will also be a steady diminution in the combined creatine and creatinine output.

The daily creatine-creatinine output has been estimated in 19 of the 20 cases in the present series, and the data are given in figs. 1 and 2, and in I and II of the appended tables, together with a very brief summary of some relevant clinical details. In the interests of brevity and convenience the figures have been given of the average daily output over a period, usually of six days. The figures for creatine have also been given expressed as a percentage of the total outputs. Figures for the creatinine index or the

output of creatinine in milligrammes per kilogram of body-weight have been included in the table. This index, however, is of more value in the comparison of different patients than in assessing improvement in the

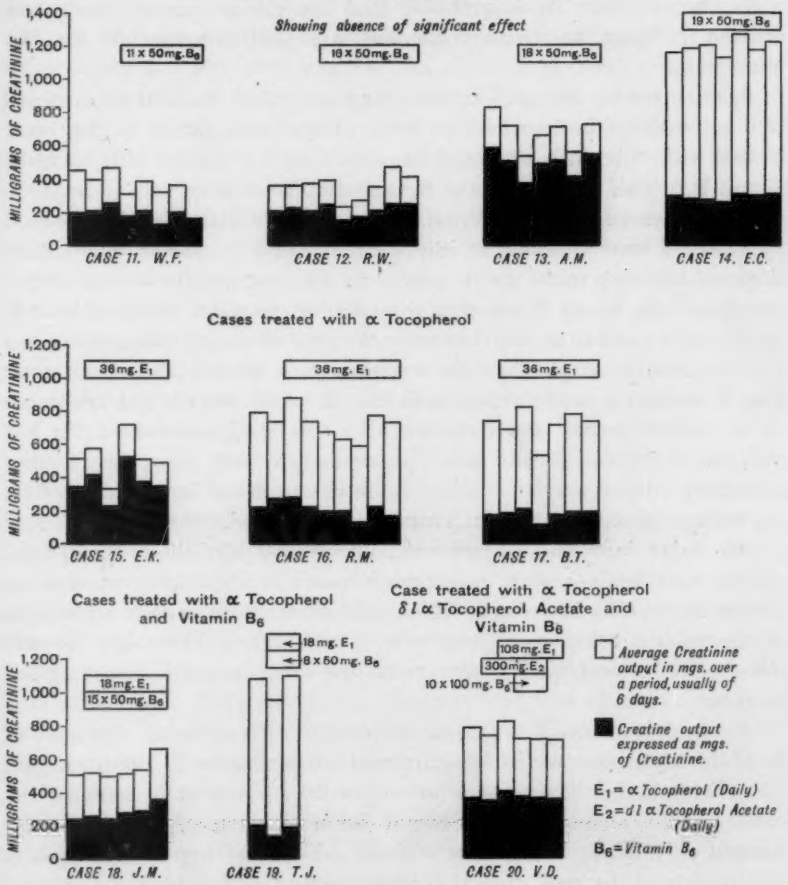
Figure 1.
Creatine-Creatinine output
Cases of Motor Neurone Disease treated with Vitamin E


Showing absence of significant effect
MILLIGRAMS OF CREATININE
CASE 1. D.N.
CASE 2. F.P.
CASE 4. A.B.
CASE 5. G.V.
CASE 6. L.C.
CASE 7. H.C.
CASE 8. L.F.
CASE 9. R.D.
CASE 10 Z.M.
INERT CAPSULES
Average Creatinine output in mgs. over a period, usually of 6 days.
Creatine output expressed as mgs. of Creatinine.
E1 = α Tocopherol (Daily)
E2 = d l α Tocopherol Acetate (Daily)
B6 = Vitamin B6 (Daily)

individual, where the daily output of creatinine is probably of the same or greater value. The creatinine index normally lies between 20 and 26 in males, and 14 and 22 in females. A considerable fall may occur in disease of muscle depending on the extent and severity of the lesion.

Both in the motor neurone disease and muscular dystrophy groups some cases have shown fluctuations in creatine and creatinine output greater than occurs in health. Three possibilities exist to account for

Figure 2.
Cases of Muscular Dystrophy
Creatine-Creatinine output
Cases treated with injections of Vitamin B_6



these fluctuations. They may be spontaneous fluctuations—the result of the disease process, they may be the result of therapy, or they may be due to incomplete collection of urine. It must be admitted that in a few of the cases the urine collection may on occasion have been incomplete.

Where this may have occurred the creatine expressed as a percentage of the total should be unaffected. The absence of any definite trend in the fluctuations makes the possibility of therapy as the cause appear unlikely. Espersen and Thomsen (1937) describe abnormal fluctuations in creatine and creatinine output in cases of muscular dystrophy, but Adams, Power and Boothby (1935) were unable to find any abnormally wide fluctuations. It is probable that the disease process itself and occasional lapses in urine collections are both responsible for the fluctuations.

Motor neurone disease.—In the group as a whole there is no evidence of improvement in creatine-creatinine metabolism, either in the cases treated with vitamin E or in the one case (Case 10) treated with vitamins E and B_6. This latter case was treated with large doses of α-tocopherol, d l-α-tocopherol acetate with vitamin B_6, together with periods in which he received inert capsules or injections of saline. Minor fluctuations occurred but they could not be related to the treatment he was receiving, and there can be no doubt that the creatine-creatinine metabolism was unaffected by either of the vitamins. Some of the other patients showed a fall in creatine output, but this was offset by a similar fall in creatinine. Case 8 showed a rather remarkable rise in both creatine and creatinine in the second period after treatment, the rise being maintained. It was difficult to get this patient to co-operate at first, and it is probable that inefficient urine collection was the cause of the initial low results. The percentage of creatine present remained unchanged.

Muscular dystrophy.—Mackenzie, Levine and McCollum (1940) have shown that rabbits with nutritional muscular dystrophy excrete an abnormal quantity of creatine which falls dramatically within a few days of the rabbits being given α-tocopherol. Verzar (1939) using massive doses of d l-α-tocopherol acetate noted the same dramatic improvement in rats.

No improvement, dramatic or otherwise, has occurred in the cases of muscular dystrophy either when treated with vitamin B_6, with vitamin E, or with both. Fluctuations in output have occurred in some of the cases, but it is noteworthy that two of the mildest cases (Cases 14 and 20) showed only minor fluctuations without evidence of improvement. It is presumably in the mild cases that improvement is most likely to occur.

Discussion.

The experimental basis for the therapy.—A sound theoretical basis exists for supposing that vitamin E might prove of value in the treatment of human muscular dystrophy. The pathological similarity of the experi-

mental nutritional muscular dystrophy and the human condition first demonstrated by Goettsch and Pappenheimer (1931) has been upheld by the majority of later workers. The experimental condition has been prevented by the addition of vitamin E to the diet either in the form of wheat germ oil, α-tocopherol, or d l-α-tocopherol acetate, and has been cured by Knowlton, Hines and Brinkhous (1939), and by Verzar (1939) using d l-α-tocopherol acetate. It should be pointed out that changes in addition to those occurring in muscle have been found and that pseudo-hypertrophy has not been noted. The theoretical background for the use of vitamin E in motor neurone disease does not rest on as firm an experimental basis. The condition first fully described by Einarson and Ringsted (1938) differs both clinically and pathologically from the human motor neurone disease. Occurring in adult rats it is characterized first by sensory changes and ataxic gait, followed by weakness and paralysis. In only two of the large number of rats was there paralysis of the fore-limbs, and in these it was only slight. Mackenzie, Mackenzie and McCollum (1940) have also noted that in the later stages of the disease, the animals develop gross static tremors and inco-ordination of the fore-limbs and head. The pathological picture is one of initial degeneration of the posterior columns with later involvement of the anterior horn cells and only inconstantly and in the final stages were changes in the cortico-spinal (pyramidal) tracts encountered. The rubrospinal tracts were not involved. Einarson and Ringsted (1938) were unable to obtain even partial cure of the paralysis with wheat germ oil, though progression could be arrested if the oil were given in the initial stages of the affection. Paralysis could be prevented only if the wheat germ oil was given soon after start-ing the deficient diet. Mackenzie, Mackenzie and McCollum (1940) obtained substantially the same results using a vitamin E concentrate. Einarson and Ringsted (1938) drew attention to the similarity of the final pathological changes found in their rats and that which would occur should tabes dorsalis and amyotrophic lateral sclerosis coexist, and they suggested that vitamin E should be tried in these two conditions. They remark that particularly favourable results could not be expected once degenerative nervous changes had occurred. It is difficult to imagine a clinical diagnosis of either of these two conditions being established without these degenerative changes.

The experimental basis for the treatment of muscular dystrophy and motor neurone disease rests on a still less secure foundation. Antopol and Schotland (1940) were prompted to employ it in muscular dystrophy by finding muscular weakness with foci of muscular degeneration in vitamin

B_6 deficient rats and the occurrence of tremors and convulsions following the administration of massive doses of the synthetic preparation.

The clinical basis for therapy.—Before detailing the results of other workers, it might be well to give a brief account of the forms in which vitamin E can be administered. Dried fresh wheat germ or the more concentrated wheat germ oil are both unstandardized and are low and variable in their vitamin E content. Vitamin E consists of a number of tocopherols, some of which have been synthesized. α-tocopherol both in its synthetic and extracted form has been used successfully in the treatment of vitamin E deficient animals. An ester of the synthetic preparation d l-α-tocopherol acetate has an equal activity and potency, and is more stable. It has been found that α-tocopherol is very much more potent than wheat germ or crude vitamin E preparations.

The existence of other factors in addition to vitamin E or α-tocopherol has been postulated by Morgulis and co-workers (1936, 1938), and by Goettsch and Ritzman (1939.) Morgulis (1938) believes that a water soluble factor present in wheat germ and yeast but not in wheat germ oil is necessary for the prevention and cure of nutritional muscular dystrophy. This contention has been criticized by Golumbic and Mattill (1940), and by Mackenzie, Milton and McCollum (1940), who have shown that α-tocopherol cured the muscular dystrophy of rats fed on diets deficient in vitamin E and the water soluble factor. The water soluble factor appears to inhibit the autoxidation and destruction of vitamin E which occurs in wheat germ oil added to the rancid diet used in the production of the dystrophy. Both groups of workers gave massive doses of vitamin B_6 as a possible source of this water soluble factor and found it completely ineffective either in the prevention or cure of the disease. Goettsch and Ritzman (1939) showed that wheat germ oil treated with ferric chloride to destroy the vitamin E content could prevent the development of muscular dystrophy in vitamin E deficient rats, but that it was unable to prevent abortion. They concluded that the capacity of wheat germ oil to prevent muscular dystrophy was not necessarily related to its vitamin E content. They found that the disease could be prevented by minute doses of α-tocopherol. Demolé (1940) has criticized this work on the grounds that sufficient vitamin E remained after the treatment with ferric chloride to prevent muscular dystrophy, but insufficient to prevent abortion. He also showed that the dystrophy could be both prevented and cured by natural and synthetic α-tocopherol.

There is, therefore, abundant evidence that α-tocopherol and d l-α-tocopherol acetate are fully effective in curing nutritional muscular dystrophy in animals.

Bicknell (1940) noted improvement in all of eighteen cases of muscular dystrophy except for six of the eleven cases which he classified as being advanced. He used 1 oz. of dried fresh wheat germ daily. He also noted suggestive improvement in two cases of amyotrophic lateral sclerosis; two advanced cases died within a short period of instituting treatment. A single case of amyotonia congenita also responded favourably. Wechsler (1940, *b*) has treated at least twelve cases of amyotrophic lateral sclerosis, three of which were too advanced to respond. One showed recovery of muscular power, whilst another responded in a remarkable manner. They were given Ephynal (d l-α-tocopherol acetate) 8 mg. by mouth daily with almost immediate improvement. A relapse followed withdrawal with further immediate improvement on restarting. The response in the others was somewhat more indefinite, but there appears to have been a remission in the progress of the disease in a number. Some doubt has been expressed as to whether one of the cases showing the marked improvement fitted clearly into the diagnosis of amyotrophic lateral sclerosis. Spies (1940) has also noted improvement in occasional cases of amyotrophic lateral sclerosis, and five cases of muscular dystrophy reported by Stone (1940) all improved.

Antopol and Schotland (1940) treated six cases of pseudohypertrophic muscular dystrophy and recorded promising results in all. When given intravenously vitamin B_6 gave immediate and dramatic improvement. The substitution of vitamin B_6 by injections of saline resulted in partial relapse, followed once again by improvement when the vitamin B_6 was resumed. Their findings await confirmation.

Our results are completely at variance with all these workers, both with regard to the value of vitamin E and of vitamin B_6 in the treatment of muscular dystrophy and motor neurone disease. We have used considerably larger doses of these vitamins, both alone and in combination, and for periods of sufficient length for improvement to have become manifest. A particularly noteworthy feature was the absence of dramatic improvement following the intravenous injection of vitamin B_6 with the exception of one case of motor neurone disease who responded equally dramatically to intravenous saline. Nor has the creatine-creatinine metabolism shown any change, in marked contrast to nutritional muscular dystrophy in animals in which a striking fall in creatinine occurs after a few days' treatment with α-tocopherol. We are unable to offer an explanation for the discrepancy between our findings and those previously reported.

SUMMARY.

(1) Ten cases of muscular dystrophy and ten of motor neurone disease have been treated with either vitamin E or B_6, or in combination, without significant improvement.

(2) In nineteen of these cases the daily output of creatine and creatinine was estimated without evidence of improvement.

(3) The experimental basis for the treatment of these conditions with either vitamin E and B_6 is discussed, and the clinical literature is reviewed.

It is with much pleasure that we thank the members of the Staff of the National Hospital for Nervous Diseases for access to their patients, particularly Dr. E. A. Carmichael, Director of the Research Unit, for much help, advice and encouragement. We have also to thank the Medical Research Council, through whose good offices we obtained materials. Glaxo Laboratories, and Merck and Co. Inc., New Jersey, have very generously given liberal quantities of vitamins E and B_6. We thank especially Mr. G. A. Stroud for performing the innumerable creatine and creatinine estimations.

Case 1.—D. N., male, aged 42. Admitted May 1, 1940, under Dr. Gordon Holmes. Discharged June 26, 1940. Died October 20, 1940.

Patient admitted with a nine months' history of weakness which commenced in the right leg and later involved other extremities. Unable to walk unaided. For eight months he had noticed " twitching " in the muscles of his limbs. No dysphagia or dysuria. No paræsthesiæ.

Generalized wasting of all four limbs—more marked distally in the upper limbs, but nowhere very extensive. Fibrillation visible over both shoulders, arms and forearm muscles and in hamstring and quadriceps groups. Deficient strength of all movements of arms and legs, most marked in dorsiflexion of feet. No sensory disturbance. Tendon reflexes uniformly exaggerated with equivocal plantar responses. C.S.F., blood, urine and W.R. within normal limits. α-tocopherol 18 mg. daily for two weeks, then 36 mg. daily until discharged.

Progress: No subjective change while under observation. Fibrillation in the tongue commenced while in hospital and there was a general increase in the patient's muscular weakness.

Discharged on 18 mg. α-tocopherol but continued to deteriorate and died October 20, 1940.

Case 2.—F. P., female, aged 56. Admitted May 23, 1940, under Dr. E. A. Carmichael. Discharged July 5, 1940. Died November 2, 1940.

Patient complained of eighteen months' history of increasing difficulty in speaking and for twelve months some difficulty in swallowing. For a few months she had been easily tired when walking. Dysarthric.

Tongue wasted, fibrillating. No obvious limitation of movement. Soft palate wasted with occasional fibrillations. Jaw reflex very brisk. No obvious wasting of musculature of trunk or extremities. Uniformly exaggerated tendon reflexes. Plantar responses not obtained. Strength normal. Gait within normal limits. No loss of sensation. C.S.F., urine, blood-count, W.R. all within normal limits.

α-tocopherol 36 mg. daily while in hospital. Discharged on α-tocopherol 18 mg. daily.

Progress: While in hospital the patient's tongue continued to waste and she developed frequent bouts of dysphagia. These increased following discharge and she died at home November 2, 1940.

Case 3.—W. C., male, aged 74. Admitted June 3, 1940, under Dr. Gordon Holmes. Discharged August 17, 1940.

(No creatine or creatinine outputs were estimated for this patient, nor was it possible to include him in the "follow-up" scheme.)

The patient claimed to be "perfectly well" until six months previously, when he slipped one day on to his back. Since that time both his lower limbs had become progressively weaker. Within the last month both upper limbs had been similarly involved. No paræsthesiæ, dysuria or dysphagia. No remissions in symptoms since their onset.

Generalized wasting of muscles of upper limbs, most marked in the dorsal interosseal group. Strength limited, particularly in all peripheral segments. In both lower limbs a similar state of affairs existed—generalized slight wasting with deficiency in power of all movements. Except for retained triceps and biceps reflexes, all tendon reflexes were unobtainable.

C.S.F., urine, blood and blood-count within normal limits.

α-tocopherol 36 mg. daily.

Progress: The patient's strength continued to deteriorate while in hospital, and on discharge he was certainly weaker than on admission. No subjective improvement.

Case 4.—A. B., male, aged 59. Admitted June 14, 1940, under Dr. Grainger Stewart. Discharged August 8, 1940.

The patient had noticed a dragging of the right foot some eighteen months before admission. Within the last year weakness had developed in the right and left wrists. Eight weeks before admission he gave up work owing to the disability. No paræsthesiæ, dysuria or dysphagia.

Slight wasting and fibrillation of the tongue. Wasting involving all the small muscles of both hands. Weakness of the upper limbs, most marked distally. No fibrillation. In the lower limbs both anterior tibial groups wasted but wasting also involved other muscles of the limbs. Strength diminished. Occasional fibrillation in calf muscles. Absent ankle reflexes but exaggerated tendon reflexes elsewhere. Bilateral extensor plantar responses. No sensory disturbance. Gait of shuffling character. C.S.F., blood and urine within normal limits.

α-tocopherol 18 mg. daily. Discharged on α-tocopherol 18 mg. daily.

Progress: No subjective or objective improvement.

Case 5.—G. V., male, aged 41. Admitted July 3, 1940, under Dr. Gordon Holmes. Discharged August 21, 1940.

Patient had a two years' history of increasing weakness of all limbs, commencing in the left arm but involving the lower limbs within the last three months. No dysuria, paræsthesiæ or dysphagia.

Wasting and weakness of all muscle groups with more involvement of the small muscles of the left hand. Occasional fibrillation seen, especially in the retrocollic group. Lower limbs thin with limitation of power of all movements, most marked in the flexor elements. Fibrillation noted. Uniform diminution of tendon reflexes with equivocal plantar extensor responses. No sensory change. C.S.F., blood and urine within normal limits.

Treatment: 36 mg. of α-tocopherol daily in hospital.

Patient discharged on α-tocopherol 18 mg. daily.

Progress: No subjective or objective improvement while in hospital. Continual

gradual deterioration in patient's condition following discharge has since necessitated admission to another hospital with increase in fibrillation and muscular weakness.

Case 6.—L. C., male, aged 40. Admitted July 30, 1940, under Dr. Purdon Martin. Discharged August 25, 1940.

Patient had a fourteen months' history of weakness of the thumb and the index finger of the right hand, gradually spreading up the arm to involve the left shoulder and hand within the last four months. Four months before admission he noted that he appeared to be unsteady on walking owing to a weakness of the right leg: left leg also weak.

Slightly fibrillating tongue with brisk jaw jerk. Weakness, wasting and fibrillation of muscles of both upper limbs, right more than left and proximally more than distally. Lower limbs within normal limits: some weakness in toes. Diminished tendon reflexes in the upper limbs and exaggerated in lower limbs, with bilateral extensor plantar responses. Gait: swinging of arms deficient. No sensory change. C.S.F., blood and urine within normal limits.

Treatment: α-tocopherol 18 mg. daily. Discharged on α-tocopherol 18 mg. daily.

Progress: No objective change. Subjectively "slightly better"—believed massage did him good. Since discharge the patient's condition has not shown any improvement but he feels better than before. He has been on Bemax 8 tablespoonsfuls daily for the last two months.

Case 7.—H. C., male, aged 39. Admitted September 9, 1940, under Dr. Gordon Holmes. Discharged October 12, 1940.

Patient gave a fifteen months' history of weakness of the limbs first involving the feet and which within the last two months affected the shoulders and hands. He had been in a number of hospitals and had improved while on massage and rest. No paræsthesiæ, dysuria or dysphagia.

Bilateral wasting of the thenar eminences. The feet were held plantar flexed. Diminished strength in all flexor movements of lower limbs, particularly of dorsiflexion of the feet. Coarse fibrillation in the quadriceps bilaterally. Tendon reflexes exaggerated in upper limbs and depressed in lower limbs. Plantar reflexes unresponsive. No sensory change. C.S.F., blood and urine within normal limits.

Treatment: α-tocopherol 18 mg. daily for three weeks: 36 mg. daily for one week. Discharged on α-tocopherol 18 mg. daily.

Progress: After two days' rest in hospital before instituting treatment patient noted that he felt "considerably better." This subjective improvement was maintained while on α-tocopherol 18 mg. daily. No objective change. α-tocopherol 36 mg. daily given during last week in hospital, and one month later Bemax 4 oz. daily added. Subjective improvement not so marked when examined on December 12, 1940. On this occasion dorsiflexion of the feet was weaker than the month before, while the gait was obviously more shuffling and laboured.

Case 8.—L. F., male, aged 62. Admitted September 9, 1940, under Dr. E. A. Carmichael. Discharged November 12, 1940.

For three years patient had noted weakness of the right arm; later of the left arm. This weakness involved the shoulder and neck muscles more than the distal groups. Lower limbs unaffected subjectively. No paræsthesiæ, dysuria, dysphagia or dysarthria. He had been a heavy drinker.

Weakness and wasting of the anterior and posterior neck muscles with involvement of the shoulder girdle muscles and to a lesser extent the distal hand groups.

Coarse fibrillation visible in deltoids, pectorals and biceps. Very considerable limitation of movement. Lower limbs: some increase in tone, otherwise normal. Tendon reflexes absent in upper limbs but present in lower limbs. Flexor plantar responses. No sensory loss. C.S.F., blood and urine within normal limits.

Treatment: α-tocopherol 18 mg. daily for four weeks. α-tocopherol 36 mg. daily for two weeks (orally). α-tocopherol 108 mg. daily for two weeks.

Discharged on Bemax 4 oz. daily and α-tocopherol 18 mg. daily.

Progress: No subjective or objective improvement. Since discharge the patient's condition has progressively deteriorated, and when last examined, January 12, 1941, he had difficulty in holding his head erect. Gait also very much more shuffling. Since admitted to another hospital.

Case 9.—R. D., female, aged 53. Admitted October 2, 1940, under Dr. Purdon Martin. Discharged December 9, 1940.

Patient had a two years' history of numbness and weakness of the left arm, then the left leg, and within the last three months of the right leg and arm. The paræsthesiæ were of a peculiar indefinite character and were aggravated by worry or excitement. No subjective loss sensation though both hands seemed weak. No dysuria, dysphagia or dysarthria.

A nervous, emotionally labile patient. Weakness and wasting of the small muscles of both hands and to a lesser extent of the forearm groups and triceps. Lower limbs: minimal weakness of distal muscles of left leg. Tendon reflexes exaggerated upper and lower limbs, with bilateral flexor plantar responses. No obvious fibrillation. No sensory change. C.S.F. and blood within normal limits. Blood count, test meal within normal limits.

Treatment: α-tocopherol 36 mg. daily for one and a half weeks. 108 mg. daily for six weeks. Discharged on α-tocopherol 24 mg. daily:

Progress: No change subjectively or objectively.

Case 10.—Z. M., male, aged 39. Admitted September 29, 1940, under Dr. Purdon Martin. Discharged December 11, 1940.

The patient gave a history of one year's aching and weakness in the right palm which had spread to involve the right shoulder in three months. Weakness of the left hand for two months. Patient had noticed twitching in the muscles of both shoulders and thighs for two months. No dysuria, dysphagia or paræsthesiæ.

Some fine fibrillation at the edge of the tongue. Jaw-jerk brisk. Weakness and wasting of shoulder and hand muscles, most marked on the right side. Wasting and fibrillation of small muscles of both hands. In the lower limbs the power was within normal limits but a considerable degree of fibrillation was noted in the extensors of the thighs. Tendon reflexes uniformly exaggerated with equivocal plantar response on the right side. C.S.F., blood and urine within normal limits.

Treatment: α-tocopherol 36 mg. daily for three weeks; 108 mg. daily for ten days. Inert capsules in similar guise for two and a half weeks: 300 mg. d l-α-tocopherol acetate intramuscularly, and 108 mg. α-tocopherol for three days orally: 300 mg. d l-α-tocopherol acetate intramuscularly: 108 mg. α-tocopherol orally, and 100 mg. daily of vitamin B_6 subcutaneously or intravenously for a further six days. Inert capsules orally and saline intramuscularly and intravenously for seven days.

Progress: This patient noted subjective improvement when on the 36 mg. of α-tocopherol daily, which was maintained when the dose was increased to 108 mg. daily. No objective change. Very much brighter. Improvement was maintained on the inert capsules for the first ten days, but after this he began to complain that he felt rather more tired and was conscious of the twitching in the legs again. (Some mild personal worries at this stage made any subjective change of doubtful value:

these were adjusted). When α-tocopherol and d l-α-tocopherol acetate were commenced, subjective improvement was again noted, and this was maintained and increased when vitamin B_6 was added. No objective change. This subjective improvement was unaffected by the later substitution of inert capsules and injections of saline. On the day before the patient's discharge he asked specifically for "one of the small capsule injections" (vitamin B_6). A dramatic subjective improvement occurred within one hour of giving 100 mg. intravenously. On the following morning an equally dramatic subjective improvement was noted when saline was given in similar capsules intravenously. Discharged on Bemax 4 oz. daily.

Case 11.—W. F., male, aged 9. Admitted April 19, 1940, under Dr. E. A. Carmichael. Discharged June 20, 1940. Diagnosis: Pseudohypertrophic muscular dystrophy.

From a very early age the child has been unsteady on his feet and had had difficulty in rising from the ground unassisted. Treated previously with glycine. No family history of the disease.

Poor muscle power in upper limbs, most marked proximally. Absent supinator longus bilaterally. Hypertrophic supraspinati. Lower limbs: typical dumpling-shape calves. Weakness of all movements of the limbs except plantar flexion. Tendon reflexes diminished in upper limbs. Absent knee reflexes but ankle reflexes present. Flexor plantar responses. No sensory loss. Gait: typical lordotic gait and characteristic attitude on rising from the prone position by "climbing up himself."

Treatment: Vitamin B_6 50 mg. every second day subcutaneously or intravenously. Discharged on α-tocopherol 18 mg. daily. Later an addition of Bemax 4 oz. daily made to diet.

Progress: No subjective or objective change noted. No appreciable difference noted whether the vitamin B_6 was given subcutaneously or intravenously. No adverse effects. The patient is now quite unable to walk unassisted.

Case 12.—R. W., male, aged 9. Admitted April 18, 1940, under Dr. E. A. Carmichael. Discharged June 26, 1940. Diagnosis: Pseudohypertrophic muscular dystrophy.

Some difficulty in walking since age of 2. The child had been inclined to stumble and fall more easily than his brothers. Unable to play games. Disability increasing. No family history of disease.

Hypertrophic tongue. Generalized weakness of upper limb muscles with absent lower half of latissimus dorsi on both sides. In the lower limbs the glutei and hamstrings were enlarged. Generalized weakness of muscles, particularly in extensors of trunk and dorsiflexors of feet. Some contracture of tendo Achillis. Generalized diminution of tendon reflexes except ankle reflexes, which were normal. No sensory change. W.R. in blood negative.

Treatment: Vitamin B_6 50 mg. subcutaneously or intravenously every second day.

Progress: No change objective or subjective noted. No response, favourable or adverse, to giving the vitamin intravenously.

Case 13.—A. H., male, aged 16½. Admitted June 21, 1940, under Dr. A. E. Carmichael. Discharged August 9, 1940. Diagnosis: Pseudohypertrophic muscular dystrophy.

Normal in every way until aged 7 when he was found to be inclined to walk on his toes with his back arched. Treated with glycine. Has been bedridden since the age of 14. No family history of the disease.

Large hypertrophied tongue. Diminished power of flexion and extension of neck and weakness in upper limb muscles, most marked proximally. Both latissimus

dorsi absent. Lower limbs: all movements limited in strength except plantar flexion of feet. Contracture of hamstrings and calf muscles. Some hypertrophy of glutei. Absent tendon reflexes except brisk ankle-jerks. Sensation normal. C.S.F., blood and urine within normal limits.

Treatment: Treated with 50 mg. vitamin B_6 subcutaneously or intravenously. Discharged on wheat germ capsules, three daily.

Progress: No improvement, subjectively or objectively. No change on giving vitamin B_6 intravenously. No change in the patient's condition since discharge.

Case 14.—E. C., female, aged 29. Admitted May 31, 1940, under Dr. E. A. Carmichael. Discharged July 15, 1940. Diagnosis: Erb's juvenile type of dystrophy.

Until aged 20 the patient led a normal life: then she began to detect some slight weakness of the upper limbs. This had progressed slowly until on admission she could not raise her arms easily above her head. No other muscular weakness. No difficulty in walking.

Flexion and extension of the neck somewhat weak. Upper limbs and trunk: slight winging of scapulæ. Deltoids deficient in bulk and strength. Triceps weak and small. Biceps somewhat weak and small. Flexion of wrist weak. Absence of supinator longi. Lower limbs: flexion and extension of knees and dorsiflexion of feet weak. Absent triceps and supinator reflexes with diminished knee reflexes. Sensation normal. C.S.F., blood and urine within normal limits.

Treatment: Vitamin B_6 subcutaneously and intravenously, 50 mg. doses every second day.

Progress: No obvious change in patient's condition. Subjectively somewhat better, though she could not indicate this by the performance of any act of strength which she had been unable to undertake prior to treatment.

Case 15.—E. K., female, aged 31. Admitted May 25, 1940, under Dr. E. A. Carmichael. Discharged July 5, 1940. Diagnosis: Erb's juvenile type of muscular dystrophy.

Patient has been well until age of 5 when she found that she could not "run around easily" like other children; she also began to have difficulty in getting up from a chair. Since then her arms and legs have steadily become weaker, especially in the last ten years. Unable to walk unassisted for one year. For a number of years she had been unable to feed herself except by resting her elbows on a table. No paræsthesiæ, dysuria or dysphagia.

Neck could not be raised unassisted from the pillow. Relatively good power in retrocollic and sternomastoid groups. Shoulders and upper limbs: some generalized wasting of all muscle groups, most marked proximally. Strength generally deficient but this was also considerably more pronounced proximally. Unable to sit up unaided. Marked lumbar lordosis. Great wasting of thigh and to a less extent of calf muscles. Strength of flexion and extension of hips and knees very deficient. Plantar and dorsi-flexion of feet relatively normal. Uniform absence of tendon reflexes. Plantar responses flexor. Sensation: nil abnormal detected.

Treatment: 36 mg. α-tocopherol daily. Discharged on 18 mg. α-tocopherol daily.

Progress: No objective change. Subjectively "better in herself" but this improvement was not evident on examination.

Case 16.—R. M., female, aged 20. Admitted April 24, 1940, under Dr. E. A. Carmichael. Discharged June 21, 1940. Diagnosis: Amyotonia congenita.

Patient's muscular weakness noticed in infancy. She crawled until age of 5 when she had first attempted to walk. Attended a special school on account of her disability when aged 7 and then she could only walk "20 yards or so" with

assistance. Stronger in the early morning. No diplopia, dysphagia or dysarthria.

In-patient of National Hospital 1939—much improvement on ephedrine gr. ½ t.i.d.

Bilateral ptosis. Slight bilateral facial weakness with crescent-shaped mouth. Wasting and weakness of trapezii and sternomastoids. Retrocollic muscles small and weak. Upper limbs: deficient bulk of muscles, especially arms, forearms and shoulders. Hands relatively normal. Considerable weakness of the arms. Extreme hypotonia. Lower limbs: wasting of glutei, thigh and calf muscles. Wasting not so marked as in upper limbs: uniform proximally and distally. Muscles flabby and hypotonic. Bilateral talipes calcaneus with deficient plantar flexion. Power greatly diminished in all movements, most marked proximally. Severe lumbar lordosis. Sensation normal. Tendon reflexes were diminished throughout. Gait: unsteady, lordotic. Walked 100 yards unassisted. Unable to rise from the prone position except by "climbing up her body."

Treatment: α-tocopherol 18 mg. daily for two weeks. α-tocopherol 36 mg. daily for three weeks. α-tocopherol 18 mg. daily: Ephedrine ½ gr. daily, one week.

Discharged on α-tocopherol 18 mg. daily: Ephedrine ½ gr. daily.

Progress: Subjective and objective deterioration while on α-tocopherol alone. Condition continued to improve on ephedrine and α-tocopherol. No change in bulk of muscles. No evidence that improvement more pronounced than when on ephedrine alone.

Case 17.—B. T., male, aged 14. Admitted July 23, 1940, under Dr. E. A. Carmichael. Discharged September 7, 1940. Diagnosis: Dystrophy.

Patient normal until age of 12 when his mother noticed that he had increasing difficulty in using his limbs. This was most marked when he attempted to walk upstairs or to rise from a chair. For a year before admission he had been taking wheat germ oil, 3 capsules daily, but he had continued to become more unsteady in his gait. No dysuria. Occasional dysphagia. Slight impediment in speech.

Arms: some limitation in power of extension of elbows and wrists. Weakness in flexion of wrists. A considerable degree of coarse fibrillation in pectorals and biceps bilaterally. Deficient muscular development, symmetrical. Legs: bilateral wasting of quadriceps, with deficient power. Deficient strength in dorsiflexion of feet. Coarse fibrillation in quadriceps groups bilaterally. Sensation normal. Tendon reflexes uniformly exaggerated with equivocal plantar reflexes.

Patient had previously been in another hospital where a diagnosis of amyotrophic lateral sclerosis had been made. C.S.F., blood and urine within normal limits.

Treatment: 36 mg. α-tocopherol daily for five and a half weeks. Discharged on 18 mg. α-tocopherol and later Bemax 4 oz. daily.

Progress: No objective change. Considerable subjective improvement which has not been maintained since the patient left hospital. When patient was seen again on January 14, 1941, no change in his condition could be detected. His mother believed that he was "somewhat weaker."

Case 18.—J. M., male, aged 21. Admitted July 30, 1940, under Dr. F. M. R. Walshe. Discharged September 11, 1940. Diagnosis: Pseudohypertrophic muscular dystrophy.

As a child, though he had been unable to run properly he played games and walked normally until the age of 14. For four years before admission he had increasing difficulty in getting upstairs. The difficulty in walking became more marked since that time.

Slight generalized weakness in upper limbs, greater proximally than distally. Some hypertrophy of supra- and infra-spinati and deltoids. Weakness more pronounced in lower limbs, particularly marked in extensors and flexors of trunk.

Some hypertrophy of vasti interni. Some contracture of tendo Achillis with well-maintained power in plantar flexors. Tendon reflexes uniformly absent except retained ankle reflexes. Plantars: flexor response. Sensation normal. Gait: walked with markedly protuberant abdomen. Could not get up from the ground unaided. C.S.F., blood and urine within normal limits.

Treatment: Vitamin B_6 50 mg. every second day subcutaneously or intravenously. α-tocopherol 18 mg. daily.

Progress: No subjective or objective change.

Case 19.—T. J., male, aged 39. Admitted August 2, 1940, under Dr. Grainger Stewart. Discharged August 30, 1940. Diagnosis: Buzzard type of muscular dystrophy.

The patient gave a two years' history of increasing difficulty in walking. No paræsthesiæ or dysuria. No stiffness of the limbs. No change in strength of upper limbs.

Cranial nerves and upper limbs: Nil abnormal detected. Lower limbs: Considerable degree of wasting of hamstring and quadriceps groups. Slight weakness of flexion and extension of thighs. Very considerable weakness in extension of knees. Both triceps and knee reflexes absent. Plantars: Flexor responses. Sensation normal.

Treatment: 18 mg. α-tocopherol daily. 50 mg. vitamin B_6 subcutaneously every second day.

Progress: No objective change. Subjectively better (the patient left the hospital after about four weeks owing to the war). He claimed then that he was less easily tired than on admission.

He has been seen a number of times since then while on 18 mg. α-tocopherol daily or wheat germ capsules. Still no objective change, but subjectively better. He feels that he is less easily tired than formerly and that he is able to undertake increased work.

Case 20.—V. D., female, aged 16. Admitted October 28, 1940, under Dr. E. A. Carmichael. Discharged November 14, 1940. Diagnosis: Pseudohypertrophic muscular dystrophy.

Patient had been normal until approximately the age of 12, when she had to discontinue games as she could not run. Since that time there had been a progressive increase in weakness of the lower limbs, most pronounced on climbing stairs. No paræsthesiæ, dysuria or dysphagia. Family history: Two other siblings of this family of nine were similarly affected—a boy aged 13 and a girl aged 14.

Slight winging of lower border of scapulæ. Deficient bulk and power in pectoralis major and latissimi dorsi bilaterally. Some weakness of deltoids and hypertrophy of supra- and infra-spinati. Some hypertrophy of calf and gluteal group bilaterally. Strength deficient in flexion and extension of hips and knees. Tendon reflexes uniformly diminished. Sensation normal. Patient unable to rise from floor except by "climbing up herself." Unable to fix shoulders when effort made to lift her with hands under arms. Gait: Waddling and lordotic. C.S.F., blood and urine within normal limits.

Treatment: 300 mg. l-α-tocopherol acetate intramuscularly daily for one week, when in addition 108 mg. α-tocopherol orally was given. Four days later in addition to 300 mg. d l-α-tocopherol acetate intramuscularly and 108 mg. α-tocopherol orally, 100 mg. vitamin B_6 was given daily.

Progress: No subjective or objective improvement.

TABLE I.—CASES OF MOTOR NEURONE DISEASE.

Case	Duration	Involvement	Improvement: Subjective	Improvement: Objective	Treatment	Days in period	Creatine mg. per day	Creatinine mg. per day	Total mg. per day	Creatinine index mg. per kilo	Creatine per cent. of total
(1)					CONTROL	6	440	783	1223	13·0	35·9
D.N.	9 mos.	+++	None	Worse	18 mg. of	6	427	672	1099	11·1	39·0
Male					Alphatoco-	6	517	878	1395	14·3	37·0
42					pherol	6	300	633	933	10·3	32·2
yrs.					daily						
					36 mg. of	6	216	576	792	9·4	27·2
					Alphatoco-	6	388	995	1383	16·1	28·0
					pherol	6	267	665	932	10·8	28·6
					daily						
(2)					CONTROL	6	292	704	996	14·3	29·3
F.P.	1½ yrs.	++	None	Worse	36 mg. of	6	327	629	956	12·4	34·2
Fe-					Alphatoco-	6	288	850	1138	17·1	25·4
male					pherol	6	196	521	717	10·7	27·4
56					daily	6	155	416	571	8·4	27·2
yrs.						6	159	548	707	10·9	22·5
(4)					CONTROL	6	167	997	1164	16·8	14·3
A.B.	1½ yrs.	++	None	None	18 mg. of	6	92	967	1059	16·3	11·5
Male					Alphatoco-	6	89	977	1066	16·3	12·0
59					pherol	6	93	794	887	13·0	10·6
yrs.					daily	6	105	858	963	14·2	10·9
						6	105	724	829	11·9	12·7
(5)					CONTROL	6	293	742	1035	11·7	28·3
G.V.	2 yrs.	++	None	None	36 mg. of	6	351	704	1055	11·3	33·3
Male					Alphatoco-	6	308	684	992	10·9	31·0
41					pherol	6	267	644	911	10·2	29·3
yrs.					daily	6	365	753	1118	11·5	32·6
						6	312	755	1067	12·4	29·3
						6	241	559	800	9·2	30·0
(6)					CONTROL	6	171	904	1075	18·3	15·9
L.C.	1 yr.	++	Doubt-	None	18 mg. of	6	155	627	782	12·7	19·8
Male	2 mos.		ful		Alphatoco-	6	187	627	814	12·7	23·0
40					pherol	6	103	649	752	13·1	13·7
yrs.					daily	6	129	728	857	14·8	15·0
						6	177	820	997	16·6	17·8
						6	216	666	872	13·5	24·8
						6	145	557	702	11·3	20·6
(7)					CONTROL	6	259	877	1136	10·7	22·8
H.C.	1 yr.	++	Moder-	None	36 mg. of	6	165	832	997	9·9	16·5
Male	3 mos.		ate		Alphatoco-	6	172	783	955	9·3	19·8
39					pherol	6	290	1121	1411	13·1	20·6
yrs.					daily	6	288	1267	1555	14·8	18·6
(8)					CONTROL	4	234	820	1054	10·9	22·2
L.F.	3 yrs.	+++	None	None	18 mg. of	6	192	716	908	9·55	21·2
Male					Alphatoco-	6	296	1052	1348	13·8	22·0
62					pherol	6	279	1010	1289	13·3	21·6
yrs.					daily	6	261	1089	1350	14·3	19·4
						3	270	863	1133	11·3	23·8
					36 mg. of	6	230	1050	1280	13·7	18·0
					α-tocopherol	5	252	1017	1269	13·3	19·9
					daily						
					108 mg. of	6	224	1030	1254	13·5	17·9
					α-tocopherol	5	264	1001	1265	13·3	20·8

Case	Duration	Involvement	Improvement: Subjective	Improvement: Objective	Treatment	Days in period	Creatine mg. per day	Creatinine mg. per day	Total mg. per day	Creatinine index mg. per kilo	Creatine per cent. of total
(9)					CONTROL	5	118	371	489	7·1	24·2
R.D. Female 53 yrs.	2 yrs.	+	None	None	18 mg. of α-tocopherol daily	5	135	442	577	8·5	23·4
						5	124	447	571	8·55	21·7
					108 mg. of α-tocopherol daily	6	102	295	397	5·65	25·7
						6	117	366	483	7·0	24·2
						6	136	404	540	7·75	25·2
						6	93	366	459	7·0	20·2
						6	86	255	341	4·9	25·2
						6	60	192	252	3·7	23·8
						5	66	284	350	5·45	18·8
(10)					CONTROL	6	231	1017	1248	13·2	18·5
Z.M. Male 39 yrs.	1 yr.	++	Fair	None	36 mg. of α-tocopherol daily	6	261	973	1234	12·8	21·2
						6	248	1004	1252	13·4	19·8
						6	250	962	1212	12·7	20·6
						5	187	1020	1207	13·5	15·5
					108 mg. of α-tocopherol daily	6	274	1004	1278	13·4	21·5
						5	200	1051	1251	14·0	16·0
					Inert capsules daily	6	249	980	1229	13·1	20·3
						6	250	889	1139	11·9	21·9
						4	293	1011	1304	13·5	22·4
					300 mg. α-tocopherol and 108 mg. α-tocopherol daily	4	321	964	1285	12·8	25·0
					As above & Vitamin B_6 100 mg. i.v. daily	5	213	863	1076	11·5	19·8
					Inert capsules daily and daily i.v. saline	6	239	880	1119	11·7	21·6

TABLE II.—MUSCULAR DYSTROPHY.

CASES TREATED WITH VITAMIN B_6.

(11)					CONTROL	6	208	245	453	9·0	45·8
W.F. Male 9 yrs.	Several years	+	None	None		6	215	182	397	6·7	53·8
						6	257	209	466	7·7	55·2
					11 injections of Vit. B_6 50 mg.	5	177	134	311	4·9	56·9
						6	207	173	380	6·4	54·5
						6	133	185	318	6·8	41·8
						6	200	158	358	5·8	55·8
						6	169	125	294	4·6	57·8

CASES TREATED WITH ALPHATOCOPHEROL.

Case	Duration	Involvement	Improvement: Subjective	Improvement: Objective	Treatment	Days in period	Creatine mg. per day	Creatinine mg. per day	Total mg. per day	Creatinine Index mg. per kilo	Creatine per cent. of total
(12)					CONTROL	6	210	150	360	6·1	58·3
R.W.	7 yrs.	++	None	Slight		6	226	136	362	5·6	62·5
Male				deterioration		6	214	160	374	6·3	56·3
9 yrs.					16 injections	6	248	145	393	5·7	63·0
					of 50 mg.	6	158	77	235	2·9	67·6
					of Vit. B_6	6	175	95	270	3·6	64·8
						6	208	146	354	5·6	58·8
						6	246	226	472	8·6	52·0
						5	251	158	409	6·0	61·3
(13)					CONTROL	6	586	245	831	4·8	70·6
A.H.	9½ yrs.	+++	None	None		6	505	217	722	4·3	70·0
Male											
16½ yrs.					18 injections	6	376	162	538	3·2	70·0
					of 50 mg.	6	491	169	660	3·3	74·4
					of Vit. B_6	6	514	198	712	3·9	72·2
						6	417	143	560	2·8	74·5
						6	544	191	735	3·7	74·0
(14)					CONTROL	6	306	860	1166	15·2	26·2
E.C.	9 yrs.	+	Slight	None	19 injections	6	286	908	1194	16·1	24·0
Female					of 50 mg.	6	280	935	1215	16·4	23·0
29 yrs.					of Vit. B_6	6	268	867	1135	15·4	23·6
						6	319	959	1278	16·7	24·8
						6	309	870	1179	15·1	26·2
						5	315	915	1230	15·8	25·6
(15)					CONTROL	6	345	170	515	3·7	67·0
E.K.	26 yrs.	+	Slight	None	36 mg. of	6	417	157	574	3·5	72·5
Female					α-tocopherol	6	226	114	340	2·5	66·5
31 yrs.					daily	6	523	187	710	4·1	73·3
						6	376	131	507	2·9	74·0
						6	359	143	493	3·2	72·8
(16)					CONTROL	6	224	559	783	16·0	28·6
R.M.	19 yrs.	++	None	None		6	269	464	733	13·3	36·7
Female					36 mg. of	6	279	598	877	17·1	31·7
20 yrs.					α-tocopherol	6	217	511	728	14·6	29·8
					daily	6	193	470	663	13·7	29·1
						6	189	432	621	12·3	30·4
						6	129	453	582	12·9	34·4
						6	219	505	769	14·4	28·5
						4	168	566	734	16·2	22·9
(17)					CONTROL	6	167	570	737	13·5	22·6
B.T.	2 yrs.	++	Considerable	None	36 mg. of	6	181	500	681	13·0	26·6
Male					α-tocopherol	6	205	617	822	14·9	25·0
14 yrs.					daily	6	112	420	532	10·2	21·0
						6	174	530	704	12·8	24·7
						6	190	584	774	14·2	24·6
						6	188	546	734	13·3	25·6

CASES TREATED WITH VITAMIN B_6 AND ALPHATOCOPHEROL.

Case	Duration	Involvement	Improvement: Subjective	Improvement: Objective	Treatment	Days in period	Creatine mg. per day	Creatinine mg. per day	Total mm. per day	Creatinine index mg. per kilo	Creatine per cent. of total
(18) J.M. Male 21 yrs.	4 yrs.	++	None	None	CONTROL	3	236	276	512	5·6	45·1
					18 mg. of α-tocopherol daily and 15 injections of 50 mg. of Vit. B_6	6	248	268	516	5·6	47·9
						6	238	261	499	5·4	47·7
						6	275	238	513	5·0	53·5
						6	282	254	536	5·3	52·5
						6	352	303	655	6·3	53·7
(19) T.J. Male 39 yrs.	2 yrs.	+	Slight	None	CONTROL	5	195	875	1070	14·8	18·2
					18 mg. of α-tocopherol daily and 8 injections of 50 mg. of Vit. B_6	6	134	817	951	13·9	14·1
						6	181	906	1087	16·3	16·6

CASE TREATED WITH VITAMIN B_6, ALPHATOCOPHEROL AND α-TOCOPHEROL ACETATE.

(20) V.D. Female 16 yrs.	4 yrs.	+	None	None	CONTROL	8	364	425	789	10·3	46·2
					300 mg. α-tocopherol injection	7	352	388	740	9·4	47·5
					300 mg. and 108 mg. α-tocopherol	3	406	414	820	10·0	49·5
					As above + 10×100 mg. of Vit. B_6 i.v.	3	370	349	719	8·45	51·5
						7	359	360	719	8·7	50·0
					108 mg. α-tocopherol	6	347	360	707	8·7	49·0

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VISUAL OBJECT-AGNOSIA WITH SPECIAL REFERENCE TO THE GESTALT THEORY.

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EXAMPLES of visual agnosia are somewhat uncommon and opportunities of studying this disorder are therefore rare. The last war, which produced a small number of traumatic cases, aroused fresh interest in the subject. The investigation of a case of gunshot wound of the occipital lobes by Goldstein and Gelb (1918) led these workers to propose an interpretation of visual object-agnosia in terms of the Gestalt theory, which was then coming to the fore as a psycho-physiological hypothesis. The "fundamental formula" of this theory has been summarized by Wertheimer (1938), one of its exponents, as follows: "There are wholes, the behaviour of which is not determined by that of their individual elements, but where the part-processes are themselves determined by the intrinsic nature of the whole." Various attempts have been made to find an adequate translation of the word Gestalt. Spearman suggests "shape," Parsons "pattern" and Sherrington speaks of the Gestalt theory as "figurism." None of these words seem to convey all the implications of "Gestalt," and in conformity with a widely current usage this word will be used in this paper. Briefly, Goldstein and Gelb, whose views are more fully discussed below, claimed to have discovered in their patient evidence of a failure of visual Gestalt formation, resulting from damage to a central physiological mechanism for the realization of visual Gestalt impressions. Owing to this defect, though the individual visual elements of objects were perceived, they were not perceived as wholes, and hence not recognized as objects. This explanation was not altogether new, for it had been foreshadowed by von Stauffenberg (1914). However, Goldstein and Gelb's theory is the first systematic exposition of a new explanation of visual agnosia since Lissauer's (1889). It has been criticized at length by Poppelreuter (1923) who rejects it, as also does Kleist (1922), though Pötzl (1928) accepts it. The subject is one of more than clinical importance since the nature of perception is of fundamental interest to psychology and to those branches of philosophy which deal with our knowledge of the external

world, though few psychologists and fewer philosophers have realized that they have anything to learn from perceptual disorders. In this paper there is reported a case of visual object-agnosia which arose at the age of 7 in a boy now 15 years old. As far as can be ascertained, in all cases of visual agnosia hitherto recorded, the disorder has arisen in adult life, and except in traumatic cases has been associated with multiple lesions or progressive arterial or neoplastic disease. The present case has offered a unique opportunity of studying the development of a child robbed of all visual recognition of objects. Tests have been devised to ascertain his capacity for perceiving visual Gestalten and the nature of visual agnosia is discussed in the light of this case.

Report of Case.

A boy with a congenital cavernous angioma of the left leg. After insertion of radium at the age of 7 he developed septicæmia and was semi-conscious for a fortnight. This illness left him with visual object-agnosia, finger-agnosia, agnosia for right and left, alexia and agraphia, and constructional apraxia. He suffers from epilepsy. On physical examination his nervous system is normal.

History.—Howard G., male, aged 15, is the only child of working-class parents. Swelling of the left leg (cavernous angioma) was observed at birth. He developed normally up to the age of 7, walked and talked when one year old, recognized and named objects at the usual age, went to school when 5 and got on well, so that by the age of 7 he could read, write and do sums.

Early in 1933 he was admitted to the London Hospital and radium was inserted into the angioma of the left leg. He was discharged and shortly afterwards he was readmitted with phlebitis of the leg and streptococcal septicæmia. He became semi-conscious and remained in this state for two weeks. When he regained consciousness he was unable to recognize objects and could no longer read, and his intelligence at first seemed much reduced. From this time he suffered from attacks of loss of consciousness. These were of two kinds. Momentary attacks, in which he appeared vacant and sometimes looked to the left, occurred as often as twice a day. More recently a few times in a year he has been subject to more severe attacks lasting about five minutes. These are preceded by an aura of "pins and needles" in the left hand. The left side of the face then becomes drawn up; the eyes are fixed, the legs jerk and there is slight foaming at the mouth. Both kinds of attacks are partially controlled by sedatives.

Physical examination.—He is righthanded. The optic discs are normal. Visual acuity canot be tested by ordinary methods, as he cannot read or recognize pictures. However he is able to see objects ½ in. in diameter at a distance of 6 yards and there appears to be no reduction in visual acuity. There is visual inattention in the right homonymous half-fields. His visual fields are full for 2/330 white and 5/330 red. The pupils and ocular movements are normal and there is no weakness of movements of the face, soft palate or tongue. There is no muscular weakness, incoordination or sensory loss in the limbs except that in the lower left limb, which is the site of a cavernous angioma extending from just above the knee to the foot,

the muscles below the knee are atrophic, weak and hypotonic and the left ankle-jerk and plantar reflex are unobtainable. Radiograms of his skull show no abnormality.

Speech, reading and writing.—His speech and articulation are normal, and his vocabulary is normal for his age. He understands spoken speech normally. He is unable to read, cannot name individual letters and cannot write.

General intelligence.—Until his illness at the age of 7 his intelligence was normal for his age, and he could read, write and do sums. Since then he has had no regular education except for a short period at the age of 9 when he went to a school for physically defective children. He made no progress there, and as the attempt to learn seemed to worry him he was withdrawn. He has derived his only education since then through his sense of hearing by listening to the wireless, especially to the talks to schools. From the wireless also he has learnt of current events, on which he is well-informed, and he repeats the news to his father when he comes home. When visited at his home he was found listening to a wireless talk on oil and repeated a description of the purification of oil by the extraction of gas, and said that petrol was obtained from the oil. He knew that lighting gas was obtained from coal. He is fond of gardening and hearing about natural history and looks after his dog, chickens and goldfish. He plays bagatelle and also plays with trains. He can count, understands the value of money and can do simple calculations, knowing the change to expect from purchases involving silver coins. He is fairly stable emotionally, though shy and inclined to be nervous at times and depressed because he is not like other children and cannot go to school. His mother thinks that his senses of hearing and smell are unusually acute.

His visual agnosia rendered many of the Binet-Simon tests inapplicable, so the following intelligence tests using other senses only were devised as additions to non-sensory Binet-Simon tests.

Q. (1).—You hear music in the street; then you hear a penny fall on the pavement.

A.—A barrel organ.

Q. (2).—You hear a bell in the street; it comes nearer and you hear a motor; then you smell burning.

A.—A fire engine going to a fire.

Q. (3).—You hear a window break, then you hear someone running away; then someone else running after the first person.

A.—I don't know.

Q. (4).—You hear a motor horn sounded; then you hear the screeching of brakes; then someone calls out and then a dog yelps.

A.—A dog has got run over.

Q. (5).—You hear a bicycle bell sounding in the street; it comes nearer and stops, and someone gives you something that feels cold and tastes sweet.

A.—An ice cream.

Q. (6).—What is the difference between a King and a President?

A.—I don't know.

Q. (7).—What is a nephew?

A.—I don't know.

Q. (8).—What is the British Empire?

A.—I don't know.

Q. (9).—What are:

(1) Charity? *A.*—You give money away.

(2) Justice? *A.*—When someone does something wrong.

(3) Goodness? *A.*—When you are excited over anything.

Q. (10).—Repeat a series of 7 figures. He failed with any number more than 3.

Owing to the special character of his disability he can hardly be allotted a mental age. The mental defect appears to be due to deprivation of the visual channels of learning and resulting lack of schooling and seclusion rather than to any defect of general intelligence. Indeed considering the severity of the agnosia the degree of intelligence and general knowledge are surprising.

Tests of Visual Perception.

Recognition of objects.—For a long time after his illness he could recognize nothing, but he has gradually re-learned to recognize some common objects with which he is daily in contact. His powers of visual recognition, however, are still very limited. Thus he recognized a fountain pen and a handkerchief, but he failed to recognize a penknife until he handled it. He called a bunch of keys a watch, and when told that it was wrong, a bracelet, but he recognized it at once when he handled it. He called a spectacle-case a purse, and when it was opened he did not recognize the glasses folded up inside until they were taken out and opened. When he was shown a piece of toffee wrapped in paper he said it was "a piece of paper wrapped up." As soon as it was placed in his hand, however, he said, "Oh, a piece of toffee." Twenty minutes later he was shown another similar piece and again failed to recognize it. When shown a child's stuffed animals, he called a white monkey a teddy bear, and failed to recognize a rabbit and a lion, but said the latter was an animal.

He cannot recognize people by sight and does not know his mother when she returns from shopping until she speaks. On one occasion an aunt, whom he sees frequently, came to the house, and before she spoke he was asked who she was. He replied: "A lady," but knew her as soon as she spoke.

Recognition of pictures.—He could not recognize the line drawings of common objects such as a cup, tea-pot, hammer, and fork, nor coloured pictures of dogs, a lion, and a man running, but when shown a picture of a donkey he said it was "like an animal." On one occasion, however, he was shown a full-length outline figure of a man used for charting sensory loss, and recognized it as a man. Failing to recognize pictures he was equally unsuccessful in matching a picture with a solid object. For example, when shown a picture of a lion and asked to choose the corresponding stuffed animal from among a lion, a white monkey, and a rabbit, he chose the monkey.

Recognition of colours.—He was asked to name the colours of skeins of wool, shown one at a time:

Colour	*Answer*
Pink	Pink
Blue	Blue
Orange	Yellow
Yellow	White
Dark blue	Black
Red	Red
White	White
Light green	Blue—no, light green
Dark green	Black or brown, no, green.
Light brown	Brown

Matching tests.—In all these tests he was extremely slow and laborious, looking repeatedly from one to another of the test objects before committing himself, and easily became fatigued.

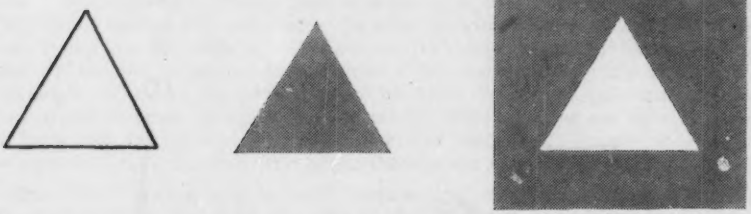
(1) Figures cut out of stout cardboard and measuring 1½ in. in diameter were used. He was shown a triangle, cross, circle, or square and asked to choose

the same figure from a group which contained them all. In this test he was almost always successful.

(2) In this test the letters of a spelling card game were used. White cards measuring 2¼ by 3½ in. bore a black letter of the alphabet 1½ in. long. He was first shown the letter M. *Q.*—What is it? *A.*—A card. *Q.*—What is on the card? *A.*—A letter. *Q.*—What letter? *A.*—I don't know. He was then shown a series of five different letters in a row, given a duplicate of one of them, and asked to pick out the same one from the series, as follows:

Series of letters	*Letter given*	*Letter chosen*
U B H S M	M	H
U B H S M	H	H
U B H S M	U	H
D L P O K	K	K
D L P O K	H	L
D L P O K	L	L

(3) Matching line diagrams. He was given a series of geometrical figures such as fig. 1 with duplicates arranged in a different order and asked to find in the right hand column the duplicate of one indicated in the left. In this test he was correct seven times out of ten.



FIGS. 1, 2, and 3.—Examples of the line, shaded and outlined geometrical figures used in the matching tests.

(4) Matching shaded diagrams. This test was the same as the preceding one except that the figures were shaded (fig. 2). He was correct once in three times.

(5) Matching line with shaded diagrams. He was asked to find the shaded figure of the same shape as a given line diagram, being correct three times out of four.

(6) Matching line with outlined diagrams. He was given the same diagrams as in test (3) except that they were surrounded with a shaded border of uniform size and shape (fig. 3) and asked to choose the outlined figure corresponding to a line diagram. In this he was correct seven times out of nine.

Thus in this series of tests of his ability to match a given shape indicated in widely different ways he was successful eighteen times out of twenty-six.

Drawing.—(1) Copying. Samples of his attempts to copy simple line diagrams are shown in fig. 4.

(2) Drawing from memory. When asked to draw various common objects, such as a dog, he said he could not do so. He offered, however, to draw a tree

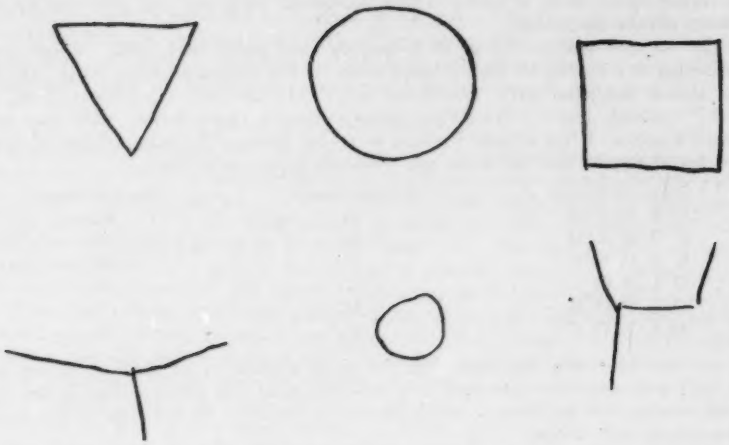


FIG. 4.—Copying. The drawings on the lower line are the patient's attempts to copy the drawings above.

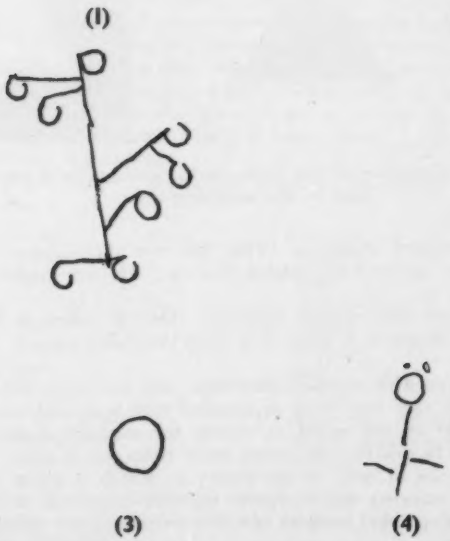


FIG. 5.—Spontaneous drawings: (1) tree; (2) boat; (3) penny; (4) man. Note that in No. 4 the only features, the eyes, have been placed outside the head.

fig. 5 (1), and then a boat, fig. 5 (2). He then drew at request a penny, fig. 5 (3), and a man, fig. 5 (4). Drawings of flowers which he had made and coloured at leisure were much more successful. They were always isolated in space, never growing or grouped in a vase, and resembled the drawings of a normal child aged 6 or 7.

Visual imagery.—I. He was asked to describe from memory various objects with which he was familiar. (1) His dog. "He is white and brown with a curly tail." (How big is he?). "He is not very big, a bit bigger than a puppy." (2) A cat. "It's got a long body and a tail. Sometimes they have a curly tail, a long tail." (That would do for a dog. How would you know a cat from a dog?) "That's easy to tell. A cat is a different colour. A cat has got claws; a dog hasn't claws." (3) A horse. "A horse stands about. It's a tall animal, that is, with four feet and a tail." (4) A motor car. "It's got four wheels and it's got windows in it, and a little seat where the driver sits and drives. I can't think of any more." (How big is it?) "They're all sizes. I've never thought." (5) The London Hospital. "It's a high building." (6) The out-patient consulting room at the hospital. "It's got a table and some chairs in it."

II. Dreaming. He experiences visual images in dreams. On one occasion he dreamed he had lost his dog (a white one). He was told it had been found, but this proved to be a black one, which bit him.

Recognition of parts of the body.—He is able to point correctly to parts of his own and the observer's body named, though he cannot distinguish his fingers by name. When shown a life-size outline drawing of a hand he recognized it, but when shown immediately afterwards the same drawing reduced to a size 2 in. by 1 in. he did not recognize it. The full size drawing was placed beside his own hand and he was asked to indicate upon it successive points touched upon his own hand. When he was allowed to see his hand touched he indicated the right point in the diagram promptly and accurately. When he was not allowed to see his hand touched he was often inaccurate, but tended to be more accurate in the case of the thumb and little finger than in the case of the other digits.

Recognition of right and left.—He understands the use of the terms right and left as reciprocally describing the sides of the body, but he does not know which are his own right and left sides and answers at random. When, however, whether rightly or wrongly, he has named one side of his own body right and the other left he applies those terms to the side of the observer's body which for the time being is to his own "right" or "left" side. Thus when he is using the terms correctly of his own body and the observer is facing him he calls the observer's right hand, left, and the observer's left hand, right, since these are on his own left and right sides respectively. If now the observer turns round and stands with his back towards the patient, the patient calls the observer's right hand, right, and the observer's left hand, left.

Spatial orientation.—When he first returned home after his illness he could not find his own way about the house. He has learned to do this, however, and he can find his way to shops and the houses of his relatives a few hundred yards away from his house. In doing so he knows where to cross the road and which way to turn, and is able to describe his route by landmarks—a shop, a tree, a street corner, &c. Beyond this short radius, however, he never goes alone, and says that if he did so he would be unable to find his way back. His judgment of absolute and relative distance is good, and he has no difficulty in traffic in judging the approach of cars or in knowing when it is safe to cross the road. He is accurate in pointing to and grasping near objects. He has no difficulty in dividing

a line in half, indicating the centre of a circle, nor in saying which of two lines is the longer.

Constructional ability.—He is entirely unable to copy simple patterns such as a triangle and a square made with matches, and he is equally unsuccessful in copying arrangements of cubical blocks, being unable even to reproduce an arrangement of four blocks placed on one another. He always recognizes his own mistakes, however, and when shown successively several incorrect arrangements and one correct one he is always able to identify the right one.

At first after his illness he could not dress himself at all, but he can now do so with some difficulty, and still makes mistakes. His mother says that he dresses "by the feel of the buttons." He does not know the right from the wrong side of a garment, but if he puts on his pullover inside out he discovers it from the fact that the "zip" fastener is in the wrong place. He wears a surgical boot on his left leg and, though he can put the laces round the hooks he cannot do so accurately, and has never learned to tie a bow.

He shows no apraxia, however, in the use of objects with which he is familiar, e.g. knife, fork, penknife, pencil, &c.

Finger Agnosia and the Body Image.

Before discussing visual object-agnosia some mention must be made of three symptoms which happened to be associated with it in this case, finger-agnosia, agnosia for right and left, and constructional apraxia.

My patient exhibited in typical form finger-agnosia as described by Gerstmann (1940), that is, he was unable to differentiate or name his fingers, indicate specific fingers on command or imitate finger movements of the examiner. As in Gerstmann's syndrome finger-agnosia was associated with inability to distinguish the right and left sides of the body and with agraphia, and with acalculia except for simple operations. Constructional apraxia was also present, but right homonymous hemianopia, described by Gerstmann as a constant feature, was absent. There was no difficulty in recognizing other parts of the patient's or the examiner's body, which supports Gerstmann's view that finger-agnosia is an isolated form of autotopognosia. An attempt was made to ascertain whether it was associated with a defective 'schema' of the hand and fingers in Head and Holmes' (1920) sense. When the patient was allowed to see his fingers touched he was able accurately to mark the spot on a full size diagram of the hand placed beside his own hand, but when he was touched on the fingers with his eyes closed and then asked to indicate the point touched on the diagram he was inaccurate, and indeed would sometimes point to the spaces between the fingers. It is inferred from this that though he could compare a spot on his hand with a spot on the diagram when both were presented together, as he could match geometrical figures in similar circumstances, a touch on his fingers with his eyes closed was not accurately related to a 'schema' of his fingers and so could not be indicated

on a diagram. This defect was not due to any impairment of cutaneous sensibility. It is noteworthy that in this test he was more accurate with the thumb and little finger than with the other fingers, which corresponds to Gerstmann's observation that the same is true of other tests of recognition of the fingers in finger-agnosia. Gerstmann attributes finger-agnosia to a lesion involving the lower part of the parietal lobe and adjacent middle occipital convolution on the left side in right-handed persons. Assuming the lesion to be cortical or immediately sub-cortical in this region there is no reason why it should *necessarily* be associated with a right homonymous hemianopia, though a massive vascular or neoplastic lesion would inevitably involve the optic radiation.

Agnosia for Right and Left.

The inability to distinguish right and left according to Gerstmann "is confined to the body sphere exclusively, that is, it does not apply to the ability to distinguish right from left in space and with respect to objects outside the body." In the present case, however, the disability extended to objects in space. The patient understood the meaning of right and left as mutually exclusive descriptions of the sides of the body, but could not say which was which. Having, whether rightly or wrongly, identified one side of his own body as right and the other as left he projected this distinction on to objects in his environment in a simple way. He divided objects by a vertical plane passing through the middle line of his own body and the middle line of the object and named the resulting halves of the object in terms of the momentary denomination of the halves of his own body. Thus he determined the right and left sides of objects in space by projecting on to them the middle line of his own body. He was unable to abstract the conception of right and left from his own body and, by generalizing it, recognize that other persons could have a right and a left side in their own right. Doubtless his failure to do this arose out of his inability to recognize that right and left possessed a constant significance for his own body. As far as can be ascertained Gerstmann's syndrome has hitherto been described only in adults, in whom it appears that the ability to recognize the right and the left sides of objects in space survives the loss of this power with regard to the patient's own body. In the present case the more profound disturbance may have been due to the associated visual object-agnosia. But since the recognition of geometrical relationships was preserved it seems more likely to be due to the fact that at the age of 7 at which the lesion occurred the abstract conception of right and left had not been stabilized.

Constructional Apraxia.

Kleist (1922) defines constructional or optical apraxia as a disorder of actions in which the spatial disposition of the action is disordered without there being an apraxia of single movements. He ascribes it, not to a loss of visual function as such, but to a disordered connection between visual, i.e. visuo-spatial, functions and the kinæsthetic engrams necessary for appropriate movements. It is thus a disorder independent both of visual object-agnosia and of visual agnosia for space. In the present case it is noteworthy that the patient fully recognized the errors in copying and block-building which his constructional apraxia caused him to make. He had therefore no agnosia for geometrical relations.

The Gestalt Theory of Visual Agnosia.

Before discussing the nature of the disorder of function exhibited by the patient reported it is necessary to review in some detail Goldstein and Gelb's theory and the criticism to which it has been subjected. Lissauer (1889) reporting a case of mind-blindness distinguished two factors in perception: (1) the act of conscious perception of a sensory impression which he called "apperception"; and (2) the act of linkage of the content of perception with other images, an act of "association." He observed that, a priori, mind-blindness might be due to an impairment of the second function alone, of the second and the first simultaneously, or of the first alone, though he considered it questionable whether the last had ever been observed. Lissauer explained the nature of "apperception" by saying that it was the awareness of an object which remained in a case of object-agnosia of the second or associative type. von Stauffenberg (1914) regarded mind-blindness as a disorder of visual perception for the production of which two factors must coincide: (1) a disorder of the central synthesis of coarse visual impressions leading to a failure of the finer "Formgestaltung"; and (2) a general injury to ideational capacity in the sense that the ecphorization of old stimulus-complexes was impossible or rendered difficult, so that the more or less incompletely formed visual elements no longer brought these into harmonic activity and therefore the further analytical process of visual recognition became impossible.

Goldstein and Gelb (1918) reported the case of a soldier, aged 24, who had received a gunshot wound in the occipital region. He had an extreme degree of concentric constriction of both visual fields. The right field extended to about 40° from the fixation point on the nasal side, 25° above, 25° on the temporal side and 25° below; the left to 33° nasally, 23° above and 18° temporally and 23° below, but the size of the test

object was not given. Visual acuity was $\frac{6}{6}$ R. and L. on one occasion and on another occasion R $\frac{5}{10}$ and L $\frac{5}{15}$. The patient was word-blind but could read if he was allowed to trace the letters by means of writing movements of his fingers. If, however, a written word was crossed by strokes at random he became confused and was unable to read it. When shown geometrical figures, whether drawings in line or shaded or coloured surfaces, he traced the shape of these by movements of his head and was then able to recognize them; and he was able to recognize simple line drawings of common objects in the same way. When shown pictures of simple scenes he did not, as a normal person would, describe the essential content of the picture but mentioned relatively unimportant details consecutively. When shown common objects he recognized them so promptly that his responses differed little from those of a normal person. The authors confessed that they found the difference of perception of geometrical figures and common objects very puzzling. When shown a geometrical figure composed of discontinuous elements, e.g. four dots arranged as a square, he failed to perceive them as a whole. When geometrical figures were exposed in the tachistoscope he did not recognize them until after three or four exposures lasting up to one and a half to two seconds. The authors concluded from these experiments that what the patient perceived visually lacked a specific typical structure. His impressions were not synthesized as in normals and he failed to receive the characteristic impression of a square, triangle, straight line or curve. He did not perceive movement as such but as a series of successive positions in space. Visual memory was tested by asking the patient to describe objects and places with which he was familiar and the authors concluded that he could not evoke visual memory images of any kind, especially that he had no visual images of letters. In spite of this, his spontaneous drawings of objects was good. He was unable to copy objects, however, and if shown an object and asked to draw it he would trace it with his head and then draw, not the object shown, but his own idea of an object of the same class.

Goldstein and Gelb considered that their patient was a pure example of Lissauer's apperceptive form of mind-blindness which was due to a defect of formation of the most primitive visual Gestalten. In other cases these might be preserved and the disorder due to a defect of higher, more complicated Gestalt impressions. In view of the preservation of light and colour perception and the absence of outspoken hemianopic field defects in their patient they concluded that the most peripheral part of the central visual apparatus in the calcarine cortex was intact and the damage

lay in a higher station within the area of visual perception, either in the occipital lobe external to the calcarine cortex or in a definite layer of the calcarine cortex itself.

Goldstein and Gelb's interpretation of their observation has been criticized by Poppelreuter (1923) who considered that in their patient there was no question of a pure mind-blindness, but that they wrongly interpreted a peculiar visual field defect. In his view Goldstein and Gelb did not prove the normality of vision within the area of the visual fields remaining, offered no adequate explanation of the nature of the "tracing" movements of their patient, and did not prove that the defect in seeing Gestalten was agnostic in character. According to Poppelreuter, experiments with the tachistoscope showed that in certain conditions normal persons exhibited (1) a perimacular field constriction; (2) a perimacular amblyopia; (3) an impairment of the ability to distinguish simultaneous visual stimuli; and (4) the perception of Gestalten without form; and patients suffering from retinal lesions causing shrinking of the macular area showed similar defects. In his opinion Goldstein and Gelb failed to distinguish a primary visual defect from an agnosia. After quoting two cases illustrating the effect on visual perception of hemianopic defects Poppelreuter goes on to criticize Goldstein and Gelb's conception of Gestalt. He points out that, psychologically, perceptual elements are not given to experience. We can speak of elements only in a physiological connection and they are discoverable only by physiological analysis. A Gestalt is only a differentiation of a part of the visual field. Applying this conception to visual form-perception even in normals we find not a geometrical structure, as Goldstein and Gelb imply, but a functional series, in which seven stages can be recognized. These are: (1) The primitive Gestalt is the visual field, pure and simple, i.e. visual extension without form. (2) In stage 2 the field becomes differentiated so that qualitatively different stimuli are experienced to left or right without form and without boundary between light and dark. (3) Next, a surface area is differentiated but without distinct dimensions. It appears neither horizontal nor vertical, but the same dimension on all sides. (4) In the fourth stage the mass possesses a direction within the visual field. (5) The fifth is the stage of indeterminate forms. There is a definite form differentiation, extension or dimension of the mass which is perceived as somewhat long, small, horizontal, &c. (6) Next comes the distinction of several separate masses within the visual fields. (7) Finally, form is perceived in the strict sense, and there is distinction of straight lines, curves, geometrical figures, &c. Thus the Gestalt principle is operative in a purely physiological sense:

already in the retina not a simple summation of single stimuli but a specific total stimulus (Gesamterregung) appears.

Poppelreuter goes on to point out that the effects of lesions of the visual afferent system may be considered according to three principles: (1) In terms of functional divisions according to the perception of (i) light and darkness; (ii) colour; (iii) space; (iv) movement; (v) direction. (2) In topographical terms, according to the parts of the visual fields affected. (3) The third principle is based on the fact that the usual field defect of cerebral origin is not amaurosis but amblyopia: it is concerned therefore with degrees of visual imperfection, not with loss of stimuli but with loss of differentiation. By applying this principle it is possible to distinguish six stages in the disintegration of visual function. (1) Stage 1 is a stage of formless and purely quantitative light perception. (2) In stage 2 an indeterminate mass is perceived but its size is largely independent of the area of retina stimulated. (3) The third stage is the stage of indeterminate forms (amorphen Formen). In this stage there is a differentiation of form and hence a Gestalt in the true sense. If an object has a principle dimension this can be recognized, but outlines are not perceived, nor a multiplicity of distinct points. (4) In stage 4 it becomes possible to discriminate two distinct lights or objects. (5) Stage 5 is described as the stage of slight amblyopia. In the ophthalmological sense the field is one of diminished visual acuity. According to Poppelreuter's theory the central part of the field exhibits properties normal in the peripheral parts. This stage merges into stage (6), that of normal vision.

Kleist (1922) agrees with Poppelreuter that Goldstein and Gelb's patient was an example of perceptive disturbance at the calcarine level and not of agnosia. Pötzl (1928) considers that Lissauer's mind-blindness represents in relative purity damage to the visual presentation of the Gestalt of concrete things. By Lissauer's mind-blindness he presumably means the associative form, present in Lissauer's patient, and not the "apperceptive" form which Lissauer merely hypothesized. Pötzl discusses Goldstein and Gelb's cases and on the whole accepts their interpretation of it, pointing out however that their standpoint is psychological rather than physiological.

The controversy over Goldstein and Gelb's patient involves two points (1) whether in fact he had visual agnosia, and (2) whether his disorder of function was primarily in the realm of visual Gestalt-production. Only if both these questions are answered in the affirmative does the further question of the relationship between the two arise.

(1) The conception of agnosia is based upon a distinction between two

phases in perception, one primary and the other secondary. In vision the primary phase is that of awareness of visual sense-data: the secondary phase is commonly held to be a non-visual associative process in which visual sense-data are linked with memory-images derived from other senses and so acquire meaning. When the terms "mind-blindness," "imperception" and "agnosia" were introduced they were applied to disorder of the second phase, the phase of awareness of sense-data being unimpaired. It was not then recognized that confusion could arise as to the phase in which a disturbance of recognition arose. The researches of the last fifty years however have shown that "seeing" in the sense of an awareness of visual sense-data is not an all-or-none process but a progressive integration and discrimination. Poppelreuter's stages have been described above. Whether or not this particular series is accepted there is ample evidence in favour of the principle. Thus Riddoch (1917) drew attention to the dissociation of visual perception due to occipital injuries, especially to the retention of awareness of movement when that of form was lost. One of his patients (Case 7), during recovery passed through stages closely corresponding to those described by Poppelreuter. "The recognition of 'something moving' came first with the ability to distinguish between light and darkness. A stationary object was next perceived as a faint blur, then its form and last of all its colour." Parsons (1927) quotes a case of Winkler's in which there was loss of form vision in homonymous half-fields. Poppelreuter's observation of a stage at which discrimination of two visual objects occurs, recalls the loss of two-point discrimination in tactile sensibility and supports the homology between visual and somatic sensibility which Riddoch points out. Holmes (1918) compares the local sign which distinguishes stimulation of different spots of the retina with the cutaneous localization of the point touched on a limb. Parsons recognizes in vision primitive "dyscritic" functions and higher "epicritic" functions.

There is also evidence that this progressive integration and discrimination of visual stimuli takes place in the primary phase of visual perception, awareness of visual sense-data. The reversal of this process by disease may result in a state in which objects are seen but are unrecognized because form-perception is impaired or because separate parts of the object are not discriminated. In Goldstein and Gelb's case the severe visual field loss indicates extensive damage to the primary visual paths and Poppelreuter appears to be right in maintaining that the perceptual defects exhibited by this patient are best explained as the result of a disorder of the primary phase of visual perception, i.e. of awareness of

visual sense-data. It is thus a disorder of apperception in Lissauer's sense, but this is not a form of agnosia as the term has hitherto been employed.

(2) The question of whether the disorder of function in this case was primarily a defect in visual Gestalt formation is more difficult to answer. From what has been said above it is clear that visual awareness comprises the presentation to consciousness of parts of the visual field as wholes. How this arises out of activity of the discrete elements of the visual cortex was one of the earliest problems investigated by exponents of the Gestalt theory. It will be recalled that Goldstein and Gelb's patient could not recognize geometrical figures or line drawings unless he traced them with his head movements, and when shown a picture he described the details of it successively rather than the picture as a whole. He recognized common objects almost as promptly as normal persons. These facts suggest that his visual field defect made it impossible for him to see the whole of a geometrical figure or picture at once. Since these wholes could not be deduced from the part he had to build up his perception of them by means of fragments seen in succession, aiding himself in the case of the figures by means of movements of the head. In the case of common objects, however, he could readily deduce the whole from the part which he could see. Since, as Poppelreuter points out, the information given by Goldstein and Gelb is insufficient to enable the visual acuity in all parts of the persisting visual fields to be ascertained it is impossible to know if this explanation is correct. It seems more probable than a defect of Gestalt-formation in view of the almost normal recognition of objects.

In my own patient there was no evidence of any defect in awareness of visual sense-data, and the agnosia was of the associative type of Lissauer. Tests consisting of matching geometrical figures, though slow and laboriously carried out, showed a high percentage of successes. He was clearly able to recognize the shape of a figure whether it was presented as an outline, a shaded surface, or a white surface with a shaded surround. Even though he did not recognize an object his awareness of its visual pattern was evidently good, as is shown, for example, by his description of a piece of toffee wrapped in paper as "a piece of paper wrapped up." There is therefore no reason to think that a defect of perception of the object as a visual Gestalt plays any part in visual agnosia of the "associative" type.

Advocates of Gestalt principles have stressed the importance of the contribution made to the recognition of an object by its visual background, so that the meaning of an object comes to be regarded as a product of the total field (Kohler, 1930), and a patient with visual object-agnosia may recognize an object when it is seen in its normal surroundings but not

otherwise (von Stauffenberg, 1914). This is doubtless true up to a point, but objects differ greatly in the constancy of their relationship to environment. An object which is seen only in one environment may not be recognized even by a normal person if artificially removed from it. No special study of this point was made in the present case.

The patient's failure to recognize line drawings of common objects, however, draws attention to the importance of the opposite principle, namely that recognition often depends upon abstraction, not only from the environment, but even from the object itself. We are so familiar from an early age with the representation of objects by outline drawings that we are apt to forget how abstract such symbols are. This act of abstraction however is not conscious: it takes place unconsciously in the process of perception. "Simple outline diagrams, serving to illustrate 'figurism,' can be rich in 'meaning'; that could hardly be unless the mind dealt in 'lines'? This so-called rivalry of contours is a master key to 'meaning' in visual perception. As far as the mind thinks spatially its thinking largely accepts 'lines' and manufactures them" (Sherrington, 1940). In the present case the matching of geometrical figures showed that shapes could be appreciated, so that the failure to recognize line drawings of objects evidently arose not from a failure to form a visual Gestalt of the shape, but from a defect in that further mental process by which the shape was identified with the object.

The Nature of Visual Object-Agnosia.

A consideration of the nature of visual perception shows that its division into the two phases of awareness of sense-data and their secondary association is an over-simplification resulting from the dissection of what is normally a unitary activity. On the one hand it is clear that in the first phase both synthetic and discriminative processes occur which are an essential preliminary to perception. It is a process of "preparatory form-synthesis" in von Stauffenberg's phrase. It is also evident that awareness of visual sense-data cannot be restricted to the first phase, for activities of the second phase enhance sensory awareness. It is a commonplace that the expert literally *sees* much more than the novice, not because his visual acuity is better but because his attention is stimulated by his past experiences. It follows that when disease prevents the second phase from occurring or impairs its efficiency, and visual agnosia results, sensory awareness also suffers. In matching tests the patient is slow and uncertain, has to return repeatedly to the model for comparison and readily becomes

fatigued. It may be true that "apperception" is the function persisting in visual agnosia, as Lissauer suggests, but it is not normal apperception.

In my patient visual memory for objects was extremely defective, and it is suggested that this was the main cause of his slow performance of visual tests as well as of his defective recognition of objects. The poverty of his visual memory was well shown by his descriptions of familiar objects from memory. In describing an animal he did not get much further than four legs and a tail. He remembered best something that literally stood out from the main structure, such as the tail of an animal. His memory for colours, like his perception of them appeared to be good. The combined effect of defective visual memory and defective evocation of other memories by visual stimuli was well illustrated by the example of the piece of toffee. When first shown this he described it as "a piece of paper wrapped up," i.e. in terms of the immediate visual sense-data only, but he recognized it at once as a piece of toffee on handling it. He then unwrapped it and ate it. Twenty minutes later a similar piece of toffee failed to awaken any memory of the recent tactile, visual and gustatory experiences and was again unrecognized. This episode also shows that there are degrees of recognition. The recognition of "a piece of paper" was correct as far as it went, but it was incomplete.

His spatial disorientation was due to the same factors as caused his object-agnosia. Only long familiarity enabled him to find his way in the immediate neighbourhood of his home, and even here though familiar landmarks played a part he appeared also to remember a route to some extent by means of distances and turnings, i.e. with the help of vestibular and other proprioceptive and even olfactory stimuli. Outside this small area however he felt completely lost, because he could not recognize the streets through which he passed. In contrast to patients with the type of spatial disorientation described by Riddoch (1917) and Holmes (1918) he had no difficulty in judging relative and absolute distances of objects, and no defect in stereoscopic vision nor in remembering a route with which he was familiar; and his difficulty was exactly the opposite of that of Wilbrand's (1892) patient who said that if she were dropped from heaven in a street in Hamburg she would recognize it perfectly but could not find her way to a single place though before her illness she knew the town well. I hope in a later paper to discuss the various forms of spatial disorientation more fully.

The patient with object-agnosia sees objects and accurately localizes them in space, but cannot recognize them. Conversely there is more than one form of agnosia for space, in which though objects are recognized

they cannot be accurately localized. The presentation to consciousness of visual objects as such and their localization in space are thus functions independent of their recognition.

Two factors contributed to the patient's disabilities in drawing and copying, his agnosia and his constructional apraxia. Defective visual imagery appeared to be responsible for the primitive content of the spontaneous drawing, while the constructional apraxia led to errors in execution in spontaneous drawing; e.g. the placing of the eyes outside the head in fig. 5, iv and still more in copying. He recognized the mistakes he made owing to the constructional apraxia. These therefore cannot be attributed to the agnosia.

In the present state of our knowledge any attempt to describe in greater detail the nature of the function lost in visual object-agnosia seems bound to fail. At the cerebral level we can localize the lesions in the brain and even picture them as interfering with linkages between different sensory fields. At the mental level we can identify certain general defects of function, but we cannot pass from the cerebral to the mental nor can we form any adequate picture in psychological terms of the process of recognition. Most accounts of agnosia either attempt to explain the mental in terms of the cerebral, or apply terms derived from consciousness to a process of which we are unconscious. Thus to speak of "a linkage of other images with the content of perception" (Lissauer) is illegitimately to introduce an anatomical conception of neural connections into a psychological explanation. On the other hand such phrases as "the ecphorization of former stimulus-complexes" (von Stauffenberg) either imply no more than that recognition depends upon past experiences or are descriptions in terms of which introspection finds no trace, for, at least in the case of common objects, there is nothing of former stimulus-complexes to be experienced in an act of recognition. Sherrington (1940) writing of the perception of a cry heard in the street says: "The physical sound in the ear was just a physical vibration. How did it generate this mental complex which seems suddenly to invade the mind full-fledged? . . . It has mental structure. How was it produced? Out of what was it constituted? Our experience does not say. It is as we experience it an already constructed complex. We have no awareness of it before then. Its beginnings are unreachable by our mind, though our mind is the only means which could reach them." Parsons (1927) puts the same point somewhat differently: "When a cat perceives a mouse he receives a vast number of sensory impressions. . . . None of these impressions taken alone or in groups, or even altogether, suffices to constitute the perception of the mouse

by the cat. The mouse is perceived as a mouse, and indeed as a particular and unique mouse, only when many or all of the sensory impressions are sifted out of their context, and selected and organized into a new complex unit. That unit is a new creation. While it retains many of the essential characteristics of its constituent sensory 'molecules' it endows them with entirely new properties. The sensations have been synthesized into a perception, the outstanding feature of which, as emphasized by Professor Stout, is the 'meaning' which it carries with it, and which is truly and scientifically described as being created by the synthesis." It may be conceded that in this sense a visual percept may rightly be described as a Gestalt and visual object-agnosia as a disorder of Gestalt formation, though Sherrington introduces an important qualification. "'Figurism' insisting on the psychical whole being more than the sum of its parts would be on safer ground if instead of *more* it say *other* than." This "other" in recognition is the meaning of an object, which may still be perfectly evoked by touch in visual agnosia or by sight in astereognosis. Object-agnosia is thus the failure to evoke meanings by a particular sensory channel, not the loss of meanings themselves.

Summary and Conclusions.

(1) The case is reported of a boy aged 15 who, at the age of 7, developed visual object-agnosia with which were associated alexia and agraphia, finger-agnosia, agnosia for right and left and constructional apraxia.

(2) The effect of his visual object-agnosia upon his mental development, spatial orientation and perception of objects, geometrical figures and pictures is described.

(3) Special tests were carried out to investigate whether the visual object-agnosia was the result of a disorder of visual Gestalt formation and it is concluded that there is no evidence for this.

(4) Interpretations of visual agnosia in terms of the Gestalt theory are discussed.

(5) Finger-agnosia, agnosia for right and left and constructional apraxia are briefly considered.

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THE SIGNIFICANCE OF LESIONS IN THE DENTATE NUCLEI APPARENTLY CONSECUTIVE TO DISEASE OF THE FRONTAL LOBES.

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THAT the cerebellum and cerebrum are functionally related has long been known, yet, even to-day, the significance of the relationship and the probable pathways subserving it are subjects about which a good deal of uncertainty still exists. From time to time isolated instances have been reported of atrophy of one cerebellar hemisphere in association with long-standing disease of the opposite cerebral hemisphere. Kononova (1912) collected and analysed these early cases to which she added four cases which she had studied personally. In contrast with the previous reports, in which the cerebral lesion had always been either a primary agenesia or a lesion dating from early life, all her patients had suffered from cerebral lesions acquired in youth or adult life. These lesions, however, were very extensive and the severity of the accompanying hemiplegia was such that no light was thrown on the part which the cerebellar deficit may have contributed to the symptomatology. The associated and, as the writer concluded, consecutive atrophy of the contralateral cerebellar hemisphere was also severe and affected in almost equal degree cortex, central nuclei and peduncles. Of the clinical evidence bearing on this problem the occasional diagnostic difficulty encountered in lesions of the frontal lobe affords an instance. Frazier (1936) in a study of 105 cases in which the frontal lobe was the site of tumour found ataxia in 49 per cent. of the cases. He concluded with the statement—"That ataxia may be caused by a unilateral or bilateral tumour of the frontal lobe even in the absence of signs of increased intracranial pressure seems to admit of no contradiction." This "frontal ataxia" can be a cause of serious confusion only in those cases in which hemiparesis is absent or inconspicuous, but that it can occur under such conditions indicates that a lesion anterior to the Rolandic area underlies the ataxia. It must not be supposed, of course, that every lesion of the prefrontal area is accompanied by ataxia

or that, even when ataxia is present, the complete picture of cerebellar disease is always simulated.

The notion that a lesion of the prefrontal cortex may be responsible for these "cerebellar" signs receives some support from the experimental findings of Aring and Fulton (1936), who carried out either hemi-decerebellation or section of one or both inferior peduncles in the monkey and, after an interval, excised either Area 4 or Area 6 of the frontal cortex. The ataxia resulting from the cerebellar or peduncular lesion was in every case temporarily abolished and permanently diminished by the excision of Area 4. Excision of Area 6, on the other hand, permanently increased the ataxia. Aring and Fulton concluded that "The anatomic basis of these relationships undoubtedly lies in the fact that the fronto-ponto-cerebellar tracts take origin from Areas 4 and 6a but principally from 6a," and they believe that the upper part of Area 6a is the area chiefly concerned in the compensation so rapidly established after hemi-decerebellation. This assumption appears to be open to some criticism in that it completely ignores the possible importance of the cerebello-cerebral pathways. Until quite recently the cortico-ponto-cerebellar tracts were quite naturally regarded as the only possible connection between the cerebrum and cerebellum for it seems to have been almost universally accepted that the fibres originating in the cerebellar dentate nucleus ended in the opposite red nucleus. It should be pointed out, however, that the observations of Risien Russell (1895) showed that in the monkey the majority of these fibres passed through the red nucleus to terminate in the ventral part of the thalamus. To-day, the experimental studies of Le Gros Clark (1936), Le Gros Clark and Boggon (1935), and Earl Walker (1937), have established beyond doubt that the fibres of the superior cerebellar peduncle terminate in a part of the ventral thalamic nucleus and that from there the cerebellar impulses could be relayed to Area 4 and, more particularly, to Area 6. It was this knowledge which determined the nature and scope of the present inquiry. Briefly, a histological study of the cerebellar dentate nuclei has been made and the findings have been correlated with the primary cerebral lesion. No attempt has been made to establish a close connection between the clinical symptomatology and the site of the cerebral lesion, for the nature of the material has not been such as to allow of precision in this respect. The more modest purpose of this communication is to show that transneuronal cell changes occur in the dentate nucleus as a result of disease in the opposite frontal lobe and, further, that these effects may and do occur when only the prefrontal region is implicated. The opportunity will be taken to discuss the bearing of these investigations on some problems of

cerebellar function and, particularly, on the relation of the cerebellum to the cerebrum.

Material and Methods.

Five cases in all have been examined. In four the prefrontal region was the seat of tumour formation and in one case, which served as a control, the parieto-temporal region was the site of a massive glioblastoma. Only the naked-eye extent of the cerebral lesion was determined. The histological examination was confined to the cerebellar dentate nuclei, to representative areas of cerebellar cortex, to the red nuclei, and to the pontine nuclei. At the beginning of this investigation it was considered advisable to employ several staining methods. Consequently in the first two cases studied (Cases 3 and 4 in the text) the dentate nuclei were cut so as to allow of frozen sections being prepared, but the greater part of each nucleus was embedded in celloidin as a preliminary to the application of Nissl's method. Some of the frozen sections were impregnated with silver (Bielschowsky's method); others were stained with Scharlach-R. Later this practice was abandoned as being too wasteful of tissue. By depending solely on the Nissl technique it was possible to make a complete examination in serial sections of the dentate nuclei. It was felt that this limitation gave advantages which would not have been obtained by applying numerous staining methods to sections cut haphazard from the nuclei. At this point reference will be made to the normal appearances of the cells of the dentate nucleus. This is the more important because the very anomalous characters of many of these cells, even in cases where organic disease of all kinds could be certainly excluded, have led certain workers to question the value of any study based on their morphological variations. It is perfectly true that isolated pyknotic cells and even small groups of three or four pyknotic shrunken cells are quite commonly seen in the normal dentate nucleus and, even more common, is the occurrence of pale or ghost-like cells. These peculiarities are, in the writer's opinion, as common in the child as in the adult and they are very evident in the dentate nuclei of the monkey (Macacus rhesus, Papio papio). However, the changes considered to be pathological in these investigations were, without question, quantitatively and qualitatively distinct from any seen in the normal dentate nucleus. Further, in every case it has been possible to compare the abnormal with the normal side and the abnormal is always at once identifiable without the least uncertainty. In this connection it may be remarked that Walker and Botterell (1937) had no difficulty in detecting retrograde cell changes in the dentate nucleus consecutive to experimental section of one superior cerebellar peduncle.

Case 1.—J. B., a woman, aged 59. Admitted to the Hôpital de la Salpêtrière (Professor Georges Guillain) in May, 1939. Her symptoms had begun three years before and consisted of intermittent headache, failure of memory and unsteadiness of gait. On examination she was found to be euphoric and slightly demented. There was a gross ataxia of the trunk with inability to maintain even a sitting posture. Muscular power was, however, well preserved and there was merely a slight increase in the tendon-jerks on the left and a left extensor plantar response. The state of all modes of sensation was normal. Radiograms disclosed well marked spiculation of the inner table in the parasagittal region of the right frontal bone. A radical operation was performed by Dr. Petit-Dutaillis but the patient survived the operation by only three weeks. At autopsy the remains of a large olfactory groove endothelioma were found. The tumour had led to the total destruction of the fore-part of the right frontal lobe. It had extended a little way across the mid-line and had compressed, but not invaded, a part of the left superior frontal convolution towards its middle third. The right precentral convolution had escaped

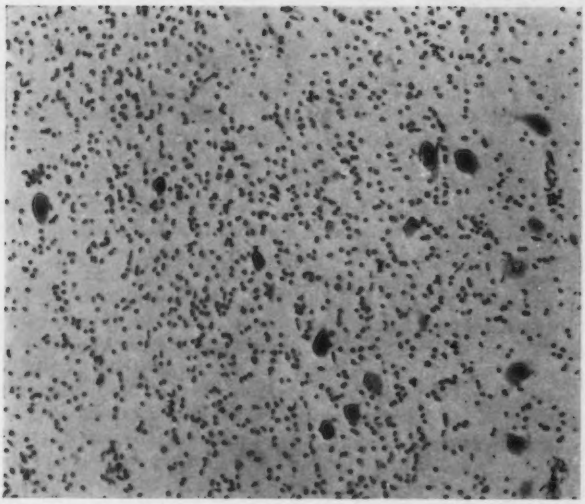

FIG. 1 (*Case 1*).—Left dentate nucleus. Note the falling out of nerve cells and the marked gliosis. In several places small aggregations of glial cells indicate the site of recently destroyed nerve cells. Nissl.

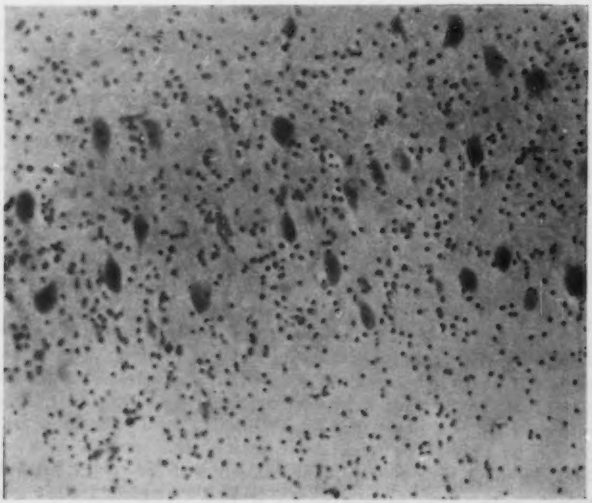

FIG. 2 (*Case 1*).—Right (normal) dentate nucleus for comparison with fig. 1. A few of the characteristic pale or ghost-like cells are seen. Nissl.

damage. There was scarcely any hydrocephalus as judged by the size of the ventricles.

The *histological examination* demonstrated that pathological cell changes were limited to, and were severe in the left dentate nucleus (fig. 1). A comparison with the right (normal) dentate nucleus (fig. 2) gives a good idea of the type and severity of the cell changes. In the affected areas not only is there a great falling out of nerve cells but the remaining cells shows all gradations of chronic cell change up to extreme shrinkage and pyknosis. A very marked gliosis is seen to accompany these cell changes and several small aggregations of glial cells indicate the site of recently destroyed nerve cells. Such an intense lesion as fig. 1 indicates is not, of course, present throughout the entire nucleus and in many regions the structure of the cells would pass as normal. Nevertheless a widespread lesion exists, for the proportion of grossly pathological cells is high in every part of the nucleus and, in addition, there is a widespread gliosis. No abnormality was detected in the cerebellar cortex, red nuclei, or pontine nuclei.

Case 2.—L. W., a man, aged 30. Admitted to the National Hospital, Queen Square (Dr. George Riddoch) on May 18, and died on August 26, 1938. The length of history was rather uncertain but probably went back to 1932 at which time he had his first fit. These fits, which were generalized, were repeated at long intervals. After a few years slight mental deterioration was noted. On examination (May, 1938) there was some impairment of memory with slight motor dysphasia. The optic discs were blurred. There were coarse tremors of both arms but chiefly of the right and there were slight weakness and increase of tendon-jerks on the right.

At autopsy a cystic astrocytoma was found. It had invaded the left frontal and parietal lobes and approached the surface near the fissure of Rolando. The basal ganglia appeared to be intact. The *histological examination* revealed changes in the right dentate nucleus which, though clearly pathological, differed in some respects from those encountered in Case 1. In general the cellular lesions were more evenly and diffusely spread whilst nowhere reaching the same degree of severity. In no areas had a complete falling out of nerve cells occurred but everywhere there were shrunken, deformed and pyknotic nerve cells. The absence of gliosis is in marked contrast to the findings in the previous case.

Case 3.—H—. P.M. Bo. 948. This and the next case will receive only brief consideration for the clinical histories are, unfortunately, lacking. Case 3 was a young adult, under the care of Professor Georges Guillain, who died in the Salpêtrière on January 6, 1934. So far as can be now ascertained she had not suffered during her life-time from symptoms suggesting focal brain disease. At autopsy a tuberculoma the size of a golf-ball was found embedded in the right frontal pole. It lay rather inferiorly and, in consequence, had destroyed the cortex and subcortical white matter of the anterior halves of the second and third frontal convolutions. On *histological examination* Bielschowsky preparations of both dentate nuclei showed that there were very gross lesions of the cells and processes in the left nucleus. In low power views there appeared to be a complete falling out of cells but with higher magnifications it was found that distorted and shrunken remains of nerve cells were almost everywhere identifiable (fig. 3). Here and there a more or less normal cell was seen but, in general, a uniform and severe lesion of almost all nerve cells was the outstanding feature of the case. In fig. 4 a section of the right (normal) dentate nucleus is shown for the sake of comparison. The remaining portions of both dentate nuclei and blocks from the cerebellar cortex, red nuclei and pontine nuclei were embedded in celloidin and sections were stained by Nissl's method. The presence of severe and widespread cellular lesions in the left dentate nucleus was confirmed. The characteristic lesion was a shrinkage and

FIG. 3 (*Case 3*).—Left dentate nucleus. There has been some falling out of nerve cells but the majority are still seen in a shrunken and structureless form. Bielschowsky.

FIG. 4 (*Case 3*).—Right dentate nucleus. Normal appearance of cells. For comparison with fig. 4. Bielschowsky.

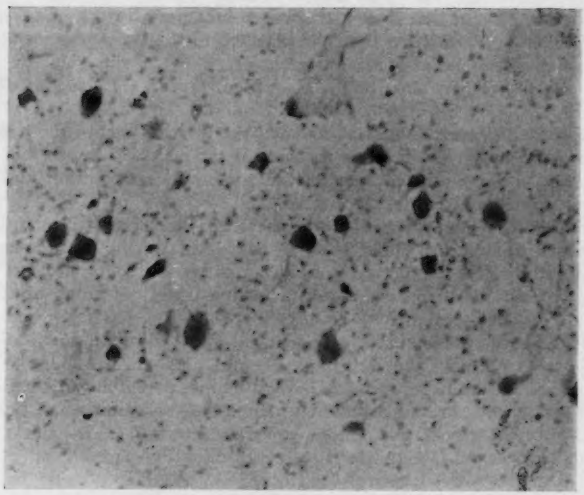

FIG. 5 (*Case 3*).—Left dentate nucleus. Note the inequality in the size of the nerve cells, the pyknosis and loss of internal structural differentiation. Nissl.

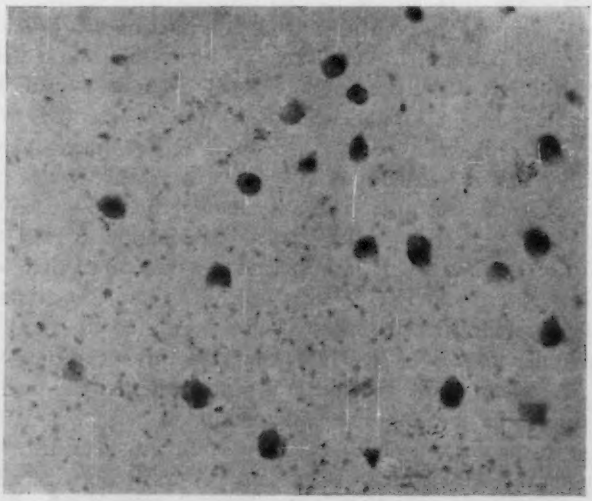

FIG. 6 (*Case 3*).—Right dentate nucleus. The appearance of the nerve cells is normal. Nissl.

sclerosis of the nerve cell (fig. 5) so that a striking contrast was afforded with the right nucleus (fig. 6). In this case there was a moderate degree of gliosis in the left dentate nucleus. No abnormality was detected in the Nissl preparations of the cerebellar cortex, red nuclei or pontine nuclei.

Case 4.—E. G., P.M. No. 1138, a woman, aged 48. Admitted to the Salpêtrière in July, 1936 (Professor Georges Guillain), and died on September 29, 1936. In this case an astrocytoma had invaded the inferior part of the right frontal lobe extending medially almost to the rostrum of the corpus callosum but as far as naked-eye examination indicated sparing the precentral convolution and the prefrontal cortex immediately anterior thereto.

Both dentate nuclei, the cerebellar cortex, the red nuclei and the pontine nuclei were examined in Bielschowsky and Nissl preparations. In the left dentate nucleus a widespread chronic cell change was present but the lesions were at a less advanced stage of development than in any of the preceding cases. Nothing abnormal was detected in any of the other regions examined.

Case 5.—L. M., P.M. No. 1115, a man, aged 64. Admitted to the Salpêtrière (Professor Georges Guillain) on February 24, and died on April 28, 1936. This was a case of glioblastoma of the left parieto-temporal region which had caused well marked sensory disturbances but in which motor symptoms had been absent. A very full study of the unusual sensory changes shown by this patient has been reported by Garcin et alii (1938). In this case histological examination of the cerebellar dentate nuclei proved entirely negative. A terminal pontine hæmorrhage precluded a satisfactory examination of the pontine nuclei, but, so far as could be made out, they and also the cerebellar cortex and red nuclei were normal.

Discussion of Results.

The observations here recorded afford conclusive proof that retrograde transneuronal cell changes occur in the dentate nucleus as a result of contralateral cerebral disease. It seems possible, however, to be a little more explicit and to assert that these remote cerebellar lesions may result from disease in the opposite prefrontal region. It must be admitted that from the nature of the material we cannot assume the complete integrity of the Area 4 but that it was substantially intact in at least two of the cases (Cases 1 and 3) seems probable. These results are, then, in accord with the ascertained facts concerning the cortical termination of the dentato-thalamo-cortical pathways. It is important to remember that while Le Gros Clark (*loc. cit.*) and Earl Walker (*loc. cit.*) found no evidence that these cerebello-cerebral tracts projected elsewhere than to Areas 4 and 6 of the cerebral cortex, Demole (1927) reported the occurrence of transneuronal cell lesions in the ventrolateral part of the dentate nucleus as a result of disease in the opposite parietotemporal cortex, and described cell changes in the dorsomedial part of the dentate nucleus in cases where the contralateral Rolandic area was affected. A case reported by Bertrand and Smith (1933) is of interest in this connection. The patient who had sustained a head injury in her youth, died at an advanced age having at

no time displayed symptoms referable to the injury. At autopsy one frontal pole was found to be the site of severe traumatic scarring and there was loss of substance in the underlying white matter. The contralateral dentate nucleus was completely atrophied. It is possible to understand the process by which this atrophy was produced only on the assumption that cerebello-cerebral pathways project on to the frontal cortex. In the present series of cases the cellular lesions in the dentate nucleus, although perhaps more pronounced in the dorsomedial part, were not limited to this portion of the nucleus and cell changes were unquestionably present in the ventrolateral portion. This evidence is, of course, insufficient to determine whether or not an exact spatial relationship exists between component parts of the dentate nucleus and particular areas of the frontal cortex. This qualification, however, in no way lessens the validity of the evidence that cerebellar influences are mediated by the dentato-thalamo-cortical tracts, and not by the cortico-ponto-cerebellar tracts. It is interesting to remember that this belief antedated by many years the discovery of the complete cerebello-cerebral pathway. The physiological experiments of Risien Russell (1897) on the effects on cortical function produced by either section of the inferior peduncle or ablation of one cerebellar hemisphere led him to conclude that the essential function of the cerebellum must be exercised in some intimate relation with the cerebral cortex. Later, Walshe (1927) pointed out that cerebellar lesions gave rise to disorders of voluntary movement only and that there is no cerebellar ataxy in a reflex preparation. He suggested that the cerebellum acts in some relation to the synthesizing function of the cerebral cortex. It should be emphasized that the acceptance of this hypothesis does not demand that the total cerebellar influence should be brought to bear on the cortical region comprised by Areas 4 and 6. A proportion of the fibres in the superior peduncle may well establish extra-pyramidal connections at the thalamic level and also, perhaps, by way of the red nucleus. If this be so it becomes possible to understand why the cerebellar syndrome, when provided by cortical disease, so often shows a greater or less degree of incompleteness.

Summary and Conclusions.

A histological examination of the dentate nuclei has been made in four cases where there was disease of one frontal lobe (three tumours, one tuberculoma) and in one case of glioblastoma of the parietotemporal region. In those cases in which the frontal lobe was affected pathological cell changes were present in the contralateral dentate nucleus, but in the

case of glioma of the parietotemporal region of the cells of the dentate nuclei were entirely normal.

No cellular lesions were observed in the cerebellar cortex or pontine nuclei and it is therefore assumed that the lesions in the dentate nuclei constituted a retrograde transneuronal degeneration. The relationship between cerebellum and cerebrum which these observations suggest is fully in accord with the recent anatomical evidence that the great majority of the fibres in the superior cerebellar peduncle establish connections via the thalamus with Areas 4 and 6 of the cerebral cortex. It also lends support to the hypothesis that cerebellar function is exerted at the cortical level and not, as has so often been supposed, through extrapyramidal pathways.

The simulation of cerebellar disease which is occasionally encountered in the course of lesions of the frontal lobe, the frequently incomplete nature of the cerebellar syndrome when thus produced and, finally, the inconstancy and variability in the intensity of the symptoms and their general tendency to regress are all more readily comprehensible on the basis of this hypothesis.

This work was carried out during the tenure of a Rockefeller Foundation Travelling Fellowship. The writer is deeply grateful for the hospitality and advice given him by Professor Ivan Bertrand, in whose laboratory these investigations were made, and to Professor Guillain and Dr. George Riddoch for giving permission to refer to their cases. Dr. J. Godwin Greenfield kindly prepared the photomicrographs.

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UNILATERAL EXOPHTHALMOS (PROPTOSIS).

CAUSATION AND DIFFERENTIAL DIAGNOSIS.

BY G. JOLY DIXON

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WHEN an eye is proptosed the direction of the protrusion may be symmetrically forwards, or it may be deviated up or down, or to either side.

PROPTOSIS WITH LATERAL OR VERTICAL DISPLACEMENT OF EYE.

A lateral, or vertical, deviation indicates that the proptosis is due to the pressure of some structure invading the orbit from one of its bony walls, or lying in the orbit outside the cone formed by the ocular muscles. Such a structure may be an exostosis or secondary carcinoma of the orbital wall, a chloromatous deposit, a secondary deposit from a left-sided adrenal tumour as described by Hutchinson (1907), a localized patch of syphilitic periostitis, or the irruption of some structure from one of the nasal sinuses such as a mucocele or a carcinoma. In a large proportion of these cases an X-ray examination will go a long way to reveal the nature of the lesion. In others the diagnosis remains extremely obscure. For example:—

Case 1.—Female, aged 37, admitted National Hospital April 15, 1940, who had been previously healthy, gave a one-year history of attacks of severe pain over the right side of the forehead. For some time she had noticed that the right eye looked "puffy" during the attacks, and more recently it was constantly "puffy." Examination showed a proptosis of 3 to 5 mm. with some downward displacement of the right eye, and in addition some bulging of the tissues around that eye. Pressure on the eye-ball immediately encountered solid resistance. There was slight right-sided papillœdema, though the vision in that eye remained $\frac{6}{6}$. The peripheral visual field was full, but the blind spot was enlarged to twice the size of that of the unaffected eye. Ocular movements appeared full, though on direct questioning she admitted she had occasional diplopia. The pupils were equal, central and showed normal reactions. There was some blunting of sensation over the distribution of the supra-orbital nerve and the maxillary division of the right 5th nerve. The cerebrospinal fluid and an X-ray of the skull showed no abnormality.

Four months later no change was noticed in her condition apart from the disappearance of the area of analgesia on the face. It was suggested that the proptosis might be due to a flat neuro-fibroma on the roof of the orbit. In support of this view it may be noted that she had three small peduncular, and two sessile, moles (not, however, very typical of Von Recklinghausen's disease).

Case 2.—Male, aged 12, admitted National Hospital November 8, 1937, under

the care of Dr. Grainger Stewart, gave two and a half months' history of diplopia and prominence of the right eye. Examination revealed moderate right-sided exophthalmos with fullness of tissues around the eye and slight ptosis of the right upper lid. There was increased resistance on attempting to push the eye back into the orbit. Vision in both eyes was $\frac{6}{6}$; the fields were full and the fundi normal. Ocular movements were full in all directions, diplopia occurred very occasionally, a few nystagmoid jerks appeared on lateral deviation of the eyes, and the pupils were equal and reacted normally. No abnormality of the central nervous system was found. X-ray examination showed dense amorphous thickening of the roof and lateral walls of the right orbit—not unlike the appearance with a meningioma on the sphenoidal ridge.

However, a history of successive fractures of the right femur at the ages of 3, 9, and 9½ years was obtained, and it was further learned that twenty months before admission to the National Hospital Mr. Muir Dickson had removed a cystic portion of this bone. A series of X-rays taken prior to operation showed the typical appearance of fibrocystic disease of the femur.

At this stage two diagnoses were possible: a meningioma of the anterior cranial fossa causing an exostosis to form in the roof of the orbit which in turn displaced the eyeball; or some unusual disease of bone which was responsible, both for the cyst formation in the femur, and the deposition of bone and sclerosing of the orbital roof. As there were no signs of intracranial disease, operative interference was deemed inexpedient, the patient kept under observation and an expectant attitude adopted.

Up to the present this patient has remained healthy and free from symptoms apart from diplopia on looking upwards. He and his parents think the proptosis has remained much the same or is possibly less marked. When seen last (October 9, 1940) there was slight proptosis of the right eye, which was very definitely on a lower plane than the left. The tissues around the eye bulged. The eye could be pushed inwards into the orbit for 1 or 2 mm. without much resistance, but solid resistance was at once met on attempting to push it upwards into a position symmetrical with the left eye. Vision in both eyes was $\frac{6}{6}$, the visual fields were full, the edges of the optic discs were slightly irregular and indistinct, but probably this was within the range of normal variation. Ocular movements were full in all directions, and diplopia only occurred on looking up—probably due to the downward displacement of the right eye. The right side of the face was slightly larger than the left—otherwise no abnormality was found.

Symmetrical Proptosis.

When the proptosis occurs symmetrically forward it is likely that it is due either to some structure lying within the cone formed by the ocular muscles, or very far back in the orbit, or possibly to a symmetrical increase in the intra-orbital contents. In such cases there are often neurological complications—the nature of these latter forms a useful basis of classification:—

(1) Cases showing papillœdema in the proptosed eye.

(2) Cases with abnormality of internal musculature, or gross abnormality of external movements of the eye.

(3) Cases with weakness of the external ocular muscles but no involvement of the ocular reflexes or vision.

Cases Showing Papillœdema in the Proptosed Eye.

Case 3.—Female, aged 5, admitted to the National Hospital under the care of Dr. Grainger Stewart in 1936 with a three months' history of gradually increasing prominence of the right eye. On examination, the grossly proptosed right eye was found to be completely blind and to have 2 mm. of sclera showing both above and below the limbus. There was gross right-sided papillœdema, and limitation of upward and outward movement of the right eye. The pupils were regular and equal, both contracting on convergence and on illumination of the left eye, but no reaction was obtainable on illumination of the right eye. X-ray examination showed the right optic foramen to be dilated to more than twice the diameter of the left. The cerebrospinal fluid contained 0·07 grm. per cent. protein—otherwise it was normal.

In a two-stage operation, Mr. Harvey Jackson found and removed a fusiform swelling of the optic nerve which extended from 2 mm. behind the globe, for 4 cm., to a point 4 mm. posterior to the optic foramen; he was able to leave the eyeball in place for cosmetic reasons. The swelling of the optic nerve proved to be an astrocytoma infiltrating the optic nerve and causing a fusiform swelling of about 1·5 cm. in diameter.

The child was re-examined four years later—when 7 mm. of proptosis (measured with exophthalmometer) of the right eye was present. The eye could be replaced easily into the orbit. The right iris was pale, the pupil was larger than the left (4 mm. and 2 mm. respectively), there were full movements of both eyes, but a marked tendency to a convergent squint, and, during movement in all directions, the right eye tended to lag behind. Both pupils contracted on convergence and on illumination of the left eye.

The right disc was china white and atrophic—its margin was circular but finely crenated at the lower border. There were three small blood-vessels, apparently a vein and two arterioles, which occupied the position of the normal inferior branches of the central artery and vein, although they were very much smaller. No other vessels were seen in the fundus.

Case 4.—Female, aged 13, admitted to the National Hospital July 29, 1938, under the care of Dr. Gordon Holmes. Proptosis was first noticed by her mother following the patient's discovery, three weeks prior to admission, that she could not read small print with the right eye. Examination revealed moderate proptosis of the right eye with swelling of the tissues. Solid resistance was at once encountered on attempting to press the eye back into the orbit. The blind spot of the right visual field was enlarged to eight times the area of the left; there was gross papillœdema on the right. Ocular movements of both eyes were full in all directions, though the right eye did not follow the same axis as the other, with resulting diplopia. The pupils were equal and gave the normal reactions. X-ray examination showed considerable enlargement of the right optic foramen.

In a two-stage operation, Mr. Harvey Jackson demonstrated, and removed, an ovoid tumour of the right optic nerve 2·5 cm. in length and 2 cm. in diameter, which proved to be an astrocytoma with remains of the optic nerve stretched over one side of it.

The patient made a satisfactory recovery, though within a few weeks after operation her proptosis increased considerably and corneal ulceration, necessitating the stitching together of the eyelids, developed.

She was evacuated from London on the outbreak of war, with the right eyelids still stitched together.

Case 5.—Male, aged 2, under the care of Mr. Moffat and Dr. Hickling at the Royal Westminster Ophthalmic Hospital. The patient's mother reported that five

weeks previously he had knocked his forehead against a chair and developed a bruise the size of a penny on his left temple; he slept normally that night, but the next morning she found that his left eye was pushed far forwards out of its socket. She had not noticed any change in its position in the interval. On examination the child proved to be most unco-operative and ill-tempered. There were 5 to 7 mm. proptosis of the left eye, the eyelids could only just close over the eye, and, on attempting to push the eye-ball back, solid resistance was encountered immediately. There was early papillœdema, and on the following week he was almost completely blind in the left eye; its pupil was larger than the right and only showed the faintest flicker of contraction on illumination, though it reacted briskly consensually.

During the next three weeks the left eye receded gradually into its normal position, but remained blind. Six weeks later the child was again seen with proptosis; the mother reported that this condition had been intermittently present from day to day, and that crying invariably made the eye protrude. On this occasion it was found possible with steady pressure to reduce the eye half-way to its normal position.

On May 23, 1940, Mr. Moffat operated and removed the left eyeball and a tumour of the optic nerve 1·5 cm. in diameter situated directly behind the eyeball.

Commentary.—In the three preceding cases the proptosis was undoubtedly due to a tumour of the optic nerve, which in two cases (3 and 4) spread down the nerve into the skull, causing enlargement of the optic foramen; it will be noted that in the case in which there was no intracranial extension of the tumour proptosis occurred suddenly. Papillœdema and some disturbance of vision occurred in the proptosed eye.

In these three cases, except for a short period in the course of Case 5, palpation of the proptosed eye demonstrated that it was firmly fixed in its proptosed position.

Case 6.—Female, aged 42, who attended the Out-Patient Clinic of Mr. Grimsdale at the Royal Westminster Ophthalmic Hospital on April 26, 1940, giving a four months' history of considerable pain in the right side of the face, followed by trismus and diplopia; right proptosis occurred as the other symptoms subsided. On examination she had considerable right-sided proptosis and swelling of the tissues around the right eye. The vision in the right eye was $\frac{6}{18}$, and in the left $\frac{6}{6}$. There was right-sided papillœdema and gross limitation of movement of the right eye; the pupils were equal and showed normal reactions. She was unable to open her mouth more than three-quarters of an inch, but reported, that a few weeks previously, this phenomenon had been much more marked. The corneal reflexes were present, and sensation on the face was normal. The movements of the eyeball rapidly recovered, and the proptosis subsided more gradually. In July the latter was hardly noticeable and the papillœdema had completely subsided.

Commentary.—The diagnosis of this case is obscure. At first it was thought to be a tumour of the optic nerve, probably a meningioma, but the spontaneous subsidence makes this view untenable. This feature and the trismus incline to the diagnosis of some inflammatory lesion in the orbit. Williamson-Noble (1926), Benedict and Knight (1923), have described inflammatory granulomata of the optic nerve and in the orbit

behind the eye, but it is impossible to state whether any of the cases described by these observers would have undergone spontaneous subsidence of the proptosis, as they had all previously come to operation.

Another feature this case showed was gross limitation of movement of the eyeball. This physical sign has been stressed by Moore (1938) and MacCallan (1938) as very typical of inflammatory conditions of the orbit.

Thus, this patient may well exemplify a case of inflammatory pseudo-tumour which underwent spontaneous resolution.

Cases Showing Gross Abnormality of Internal and External Movements of the Eyes and Some Visual Disturbance.

Case 7.—Male aged 40, admitted June 19, 1939, to the National Hospital under the care of Dr. Gordon Holmes, developed severe pain over the left side of the forehead one month prior to admission, followed three weeks later by diplopia and drooping of the left upper lid. The left eye was proptosed, there was some œdema, swelling and redness of the peri-orbital tissues; vision was $\frac{6}{6}$ in both eyes, though a small central scotoma was demonstrated on the left, the fundi showed no abnormality. There was ptosis and limitation of upward, downward and inward movement of the left eye. The left pupil was larger than the right and more sluggish in its reactions. A month after admission the patient suddenly developed a complete 3rd nerve palsy (ptosis with internal and external ophthalmoplegia).

He was readmitted September 25, 1939, four months after the first symptom, in coma, and died within twenty-four hours. Autopsy showed a subarachnoid hæmorrhage and an aneurysm the size of a bean on the terminal portion of the left internal carotid which was pressing back into the cavernous sinus.

Case 8.—Male, aged 26, admitted December 14, 1935, to the National Hospital under the care of Dr. Brinton, stated that he had had four accidents resulting in concussion at the ages of 5, 16, 22 and 23 respectively; that following the first, his "right eye turned in," and that during the year before admission he had wakened on most mornings with a severe throbbing headache accompanied by nausea, also he had had transient attacks of loss of vision which usually followed stooping, and for the last three weeks he had seen everything double. He had also noticed a machine-like buzzing in his head. On examination he proved to have definite left-sided proptosis. The vision in both eyes was $\frac{6}{6}$ and the fields full. There was bilateral papillœdema, variable nystagmus and variable palsy of both external recti; otherwise the ocular movements were full and the pupils showed no abnormality.

Lumbar puncture revealed a straw-coloured fluid with 0·560 grm. per cent. of protein. X-ray examination showed erosion and deepening of the pituitary fossa, and, when a ventriculogram was performed, the lateral ventricles were seen to be irregularly filled and displaced to the right. Dr. Russell Reynolds suggested that such findings were consistent with a tumour between the ventricles.

On December 20, 1935, a left fronto-temporal decompression was performed; no tumour was found. The patient made a satisfactory recovery and, five years later (September 18, 1940), he stated that he was practically free from symptoms since the operation. On examination, there was a bulging, though not very tense, left temporal decompression; the left eye was 7 mm. proptosed (exophthalmometer), and was felt to pulsate in unison with the heart beat and to be easily reducible into the orbit. Compression of the left carotid artery abolished the pulsation. The tissues around the eye were swollen. Vision in both eyes was $\frac{6}{9}$. There was a right-

sided homonymous hemianopia (first discovered September, 1937) coming to within 5° or 10° of the fixation point. Both optic discs were flat, though there was some blurring of the nasal margins. The pupils showed no abnormality. With a Maddox rod it was possible to demonstrate slight upward and outward limitation of movement of the left eye. X-rays demonstrated the bony walls of the left orbit to be intact.

On auscultation of the head a machine-like murmur could be heard over the left eye, the forehead, the decompression and both temples.

An aneurysm of the left internal carotid artery, similar to that found at autopsy in Case 7, would account for all the neurological signs found in this patient—also it would appear on ventriculography as a tumour between the ventricles.

Cases of intracranial aneurysm which produce a machine-like murmur are usually assumed to be of the arterio-venous type, though the evidence for this is scanty. Thus in this case, the diagnosis rests between an arterio-venous aneurysm of the internal carotid and cavernous sinus, or a simple aneurysm of the terminal stage of the former.

Case 9.—Male, aged 24, admitted to the National Hospital July 22, 1938, under the care of Dr. Gordon Holmes. The previous April he had sustained a fracture of the base of the skull and concussion; six days after the accident he complained of diplopia and was found to have left-sided proptosis. Some months later he suffered from a series of recurrent attacks of confusion, during the course of which he experienced pain and a sense of pulsation in the head. On examination, he was found to have considerable proptosis of the left eye and slight proptosis of the right. The eyes could be pressed back easily into the orbits without resistance. There was swelling and œdema of the tissues of the left orbit. Right vision was $\frac{6}{6}$, left vision $\frac{6}{12}$. Both fields were full. There was a right external rectus palsy and some limitation of movement of the left eye in all directions; the left pupil reacted less and more sluggishly to light than the right. A machine-like murmur could be heard on auscultation over the left eyeball, forehead and temple. This became less on compression of the left carotid.

On September 8, 1938, Mr. Harvey Jackson tied the left internal carotid, which resulted in partial recession of the proptosis and recovery of the ocular movements.

The symptoms in this case are probably due to an arterio-venous aneurysm in the middle cranial fossa.

Case 10.—Male, aged 57, admitted March 26, 1935, to the National Hospital under the care of Dr. Gordon Holmes, stated that twenty months previously he had had a road accident in which he sustained concussion and multiple fractures, including one of the base of the skull. Immediately on regaining consciousness he heard a murmur in his head, which had been present ever since. Soon afterwards he had developed diplopia, which had been present till the last month, when, following an attack of severe pain on the right side of the head, he had lost the sight of his right eye. On examination, there was a right-sided proptosis of over 3 mm. which was easily reducible. The tissues around the eye were swollen, and there was a hæmorrhagic glaucoma and congestion of the conjunctiva. Movements of the proptosed eye were limited in all directions, but especially outwards. A blowing systolic murmur could be heard on auscultation over both temples; this was temporarily abolished by pressure over the carotid tubercle.

Owing to the presence of glaucoma, Mr. Williamson-Noble removed the proptosed eye, without encountering any increased vascularity or other abnormality of the orbit.

This is almost certainly a case of an aneurysm of the middle cranial fossa—probably an arterio-venous aneurysm.

Commentary.—In Cases 7 to 10 an aneurysm, or arterio-venous aneurysm, of the terminal portion of the internal carotid artery was accompanied by proptosis and limitation of movement of the corresponding eye. The proptosed eye could be pushed back easily into the orbit.

Case 11.—Male, aged 37, admitted April 26, 1938, to the National Hospital under the care of Dr. Gordon Holmes, gave an eighteen months' history of recurrent headaches followed in the final nine weeks of this period by diplopia and blurring of vision in the left eye. On examination, there was obvious proptosis of the left eye, but the eyeball could be displaced back into the orbit without resistance. Right vision was $\frac{6}{6}$, left vision $\frac{6}{6}$, but there was bitemporal hemianopia to $\frac{1}{2000}$ test object. The left upper lid did not retract fully, and there was limitation of upward, downward and inward movement of the left eye. The left pupil was dilated and immobile; the reactions of the right were normal.

On May 17, 1938, Mr. Harvey Jackson at operation demonstrated, and partially removed, a chromophobe adenoma of the pituitary which projected between the optic nerves; he also incised the diaphragm sella to allow for upward expansion of the tumour. The proptosis rapidly subsided, and the movements of the eye, both internal and external, also returned to a large degree.

In December, 1939, after some return of the headache, he woke one morning to find an immense proptosis of the left eye. On being questioned he admitted that it might have been slightly prominent for some time past. When seen three weeks later, the left eye was found to be at least 10 mm. proptosed and absolutely irreducible. The tissues of the orbit were swollen, and the conjunctival sacs were everted and œdematous. Right vision was $\frac{6}{12}$, left vision $\frac{6}{9}$; the left disc could not be seen properly. There was gross limitation of all movements of the left eye; the pupil was larger than the right and was less active in reacting to light or on attempting convergence.

His condition now, in September, 1940, showed very little change. The proptosis was 15 mm. (exophthalmometer), the vision of the proptosed eye had deteriorated to $\frac{6}{60}$. Both discs were pale, but otherwise normal. Some movement of the eyeball remained, but the pupil was fixed and dilated.

Commentary.—It is probable that proptosis in this case, as in Cases 7 to 10 is due to the presence of an abnormal structure in the middle cranial fossa. Whether the immediate cause is venous obstruction, or paralysis of the ocular motor muscles by pressure on their motor nerves, will be considered later.

The following case, though not belonging to this section, is probably most usefully considered here.

Case 12.—While attempting an alcohol injection of the gasserian ganglion for the relief of tic douloureux in a male patient of 62 years of age, the needle was passed inadvertently into the orbit through the inferior orbital fissure, although no alcohol

or other foreign substance was injected. A proptosis of about 10 mm. developed in the space of two minutes. The next day the eye was still protruded 10 mm., the protrusion being irreducible. There was bluish-black swelling of the tissues around the eye, rendering opening of the eyelids difficult. Visual acuity and the fundi were normal. Ocular movement was reduced in all directions, the pupils were equal in size and showed normal brisk reactions. The patient made an uninterrupted recovery in about two weeks.

Commentary.—This case is of interest as it shows that the blood supply of the orbit is sufficient in volume and pressure to produce the most marked proptosis in a few minutes if free bleeding occurs into the tissues. Now, if venous return from the orbit is seriously impaired, the same forces are available to produce proptosis, provided, of course, that the venous channels are sufficiently distensible to allow of proptosis.

Cases Showing Weakness of the External Ocular Muscles but no Involvement of Internal Muscles or of Vision.

Case 13.—Male, aged 51, admitted May, 1940, to the Out-Patient Clinic at the Royal Westminster Ophthalmic Hospital under the care of Mr. Wolff and Dr. Hickling, stated that since 1918 he had been liable to recurrent conjunctivitis; that during the last seven months he had been constantly told that his left eye was prominent, and that he has a tendency to keep it closed. On examination, he was found to have a left proptosis of about 5 or 6 mm. and increased pigmentation of tissues around the left eye. No resistance was met on pushing the eye back into the orbit. Vision and fundi were normal. Ocular movements were of full range, though, on reaching complete lateral deviation, nystagmoid jerks appeared in the left eye, and examination with a Maddox rod showed limitation of internal and downward movement of the same eye. The palpebral fissures and pupils were equal on the two sides, and the latter showed normal reactions. He admitted that he was a highly-strung individual, and eight months' subsequent observation, including nineteen days in hospital, showed that, though he tended to sweat abnormally in hot weather and developed a tachycardia and fine tremor on excitement, these signs rapidly disappeared after resting for an hour or two.

Enlargement of the thyroid was not observed at any time, and his basal metabolic rate showed only a 5 per cent. increase on the normal. The patient and his relatives were of the opinion that directly after his discharge from hospital his left eye was less prominent than it had previously been, but, gradually, during the following five months, it again became prominent, though his health otherwise remained excellent and he lost no weight. Unfortunately no opportunity to substantiate this observation occurred.

Commentary.—This case showed many of the features of Graves' disease—on the other hand the exophthalmos was out of all proportion to the other signs of thyroid intoxication, and was confined to one eye. Brain and Turnbull (1938) collected a series of such cases and described them under the heading of Exophthalmic Ophthalmoplegia. Many of their cases had been followed for upwards of twenty years without their having developed clinical Graves' disease, and others showed evidence of myxœdema due to past thyroidectomies.

Case 14.—Male, aged 51, admitted May 3, 1940, to the Out-Patient Clinic at the Royal Westminster Ophthalmic Hospital under the care of Mr. Viner and Dr. Hickling, gave a twelve months' history of right-sided proptosis and three months' diplopia. On examination, there proved to be some proptosis of both eyes, much more marked on the right. Little resistance was encountered on pushing the right eye back into its normal position. Vision and fundi were normal. There was limitation of movement of the right eye in all directions, but no abnormality of pupils nor of palpebral fissures. The thyroid was very slightly enlarged, there was a tachycardia of about 110 and a fine tremor, both of which subsided after a few hours in bed. The basal metabolic rate was within the normal range, the patient had lost no weight, and otherwise felt well.

During the subsequent five months the diplopia and proptosis became gradually more marked. Otherwise his condition remained stationary.

This is probably another example of exophthalmic ophthalmoplegia.

Case 15.—Male, aged 60, attended the Out-Patient Department of the National Hospital under the care of Dr. Purdon Martin, suffering from early progressive muscular atrophy. In addition he stated that since childhood he had noticed that his right eye was more prominent than the left and that he could not see properly with it. On examination, he was found to have between 2 and 4 mm. of proptosis of the right eye. The eye tended to turn out and up in much the same position as Case 12. Both eyes could be pushed back into the orbit against very little resistance, and such treatment resulted in their both reaching the same position. Sight was defective in the right eye, from a high degree of myopia—16 D. Both visual fields were full. The patient was unable to rotate the right eye internally more than 5° to 10° from the antero-posterior position, and with a Maddox rod, limitation of outward and up and down rotation of this eye could be demonstrated. The pupils were circular, with equal diameters of about 3 mm., and reacted normally.

This was thought to be a case of external ophthalmoplegia of over fifty years' duration.

Cases Showing No Visual Phenomena or Nerve Palsies.

Case 16.—Male, aged 47, admitted July 26, 1940, to the Out-Patient Clinic, Royal Westminster Ophthalmic Hospital under the care of Mr. Penman and Dr. Hickling, stated that his friends had commented on the prominence of his left eye for about nine months.

There was 3 or 4 mm. of left proptosis; the eye could be pushed back into normal situation against some resistance. Vision, fundi and ocular movements were normal, the pupils were both large but their reactions normal. The left palpebral fissure was larger than the right, and the left upper eyelid tended to lag behind the eyeball on looking downward. On the first examination he had a red, flushed face, excessive sweating, a bounding pulse of 108, and a blood-pressure of 170/85; on subsequent examination the proptosis was less obvious (probably due to less lid retraction), the pulse about 80, and there was no sweating and flushing of the face. At no time did he feel ill or lose any weight.

Commentary.—Moore described four cases similar to this, also showing retraction of the upper lid. Three of these developed thyrotoxicosis; Pochin (1939) described a further two; one suffered from this disease and the other subsequently developed it.

Thus, thyrotoxicosis would appear to be a relatively common cause

of mild unilateral proptosis which is almost always accompanied by retraction of the upper lid and no other abnormality of the cranial nerves.

Case 17.—Female, aged 40, admitted January 18, 1940, to the National Hospital under the care of Dr. Grainger Stewart, with one month's history of gradual, painless protrusion of the right eye. On examination, the right eye proved to be 5 to 10 mm. proptosed. The tissues around it were puffy and swollen. The eye could be pushed back into the orbit about half-way towards the normal position against a cushion-like resistance. The patient had a high myopia, but otherwise her vision and fundi in both eyes were normal—there was no disturbance of ocular movements or pupillary reactions. An X-ray showed considerable diffuse thickening of the lesser wing of the sphenoid and the bones around it. The cerebrospinal fluid was of normal pressure and composition apart from a protein of 0·055 grm. per cent.

At operation on February 27, 1940, Mr. Harvey Jackson demonstrated, and removed, a meningioma *en plaque*, about half an inch thick, situated over the outer portion of the lesser wing of the sphenoid. He decompressed the orbit, whose roof and posterior walls were considerably sclerosed and thickened.

When she was seen six months later, the proptosis was as before (9 mm. by exophthalmometer), but now completely irreducible. No change had occurred in the vision, fundi or pupil reactions, though it was possible, using a Maddox rod, to demonstrate a defect in outward and upward movement of the right eye.

Commentary.—If in this case (Case 17) the original proptosis was due to obstruction of venous and lymphatic return through the sphenoidal fissure, it would explain the partial reduction of the proptosis possible at the first interview, the escape of the optic nerve and the absence of any portion of the tumour from the orbit. Subsequent occlusion of further lymphatic and venous channels due to post-operative trauma rendered the proptosis permanently irreducible, without, however, interfering much with the sight or movement of the eye. Another possibility is that inter-orbital spread of the growth had occurred since operation.

Discussion.

It will be seen from a study of the foregoing cases that unilateral exophthalmos may result directly from the enlargement of some structure within the orbit, or invading the orbit. If either of these is the cause, it will be found on palpation of the eyeball that solid resistance is at once encountered on attempting to push it back into the orbit. Further, the direction of proptosis depends on the position of the structure pushing the eye out; if this lies in the roof of the orbit the direction of the proptosis is downwards, and more resistance is felt on attempting to push the eye upward than backward. If, however (as in Cases 3 to 5), the abnormal structure lies within the cone of external muscles of the eyeball, the proptosis will occur symmetrically forwards, and greater resistance will be felt on pushing the eye back into the orbit than in any other direction.

Tumours or other space-occupying structures in the middle-cranial fossa may also cause unilateral proptosis ; six such cases are here described (Cases 7 to 11, and Case 17). In these cases the proptosis occurs without any upward or downward displacement of the eyeball, and in the majority of these cases palpation of the eyeball elicited the fact that it was very easily pushed back into its normal position. An interesting phenomenon was observed in one or two of these cases—first pressure on the eyeball appeared to meet solid resistance, then if this was continued it was found that the eyeball had receded to its normal position, although it immediately protruded when the pressure was removed ; on immediately subsequent examinations the eyeball could be pushed back with very little resistance. As this phenomenon was most marked in Case 8, in which pulsation of the eyeball was easily felt, it was thought to be due to the emptying from the orbit of excessive blood and lymph.

It is probable, that in these cases (Cases 7 to 11, and Case 17), venous and lymphatic obstruction played a large part in the production of the proptosis. Another possible factor is paresis of the external muscles of the eyeball due to pressure on the 3rd, 4th and 6th cranial nerves where they lie in the wall of the cavernous sinus.

In Case 11, the growth of the pituitary tumour probably distorted the fibrous partition between the sella turcica and the cavernous sinus, causing venous obstruction to the orbit, and paresis of the internal and external muscles of the eyeball. Marine (1931) described a pituitary hormone which caused bilateral exophthalmos when administered in excess to rabbits. It is just possible that this substance was excreted in abnormal quantities by the tumour and was a factor in producing the proptosis.

Proptosis may also result from paralysis of the external ocular muscles. This is seen in some cases of myasthenia gravis—though as a rule the proptosis in this condition is bilateral. In the present series, three cases of ophthalmoplegia are described which showed unilateral exophthalmos ; and the case of the child who showed 7 mm. of unilateral proptosis four years after a glioma of the optic nerve had been successfully removed. In these cases, pressure on the proptosed eye immediately reduced it to its normal position, though again it was thought that possibly slightly more resistance was felt on the first examination than on subsequent ones.

In the case of the child, permanent lengthening of the external muscles of the eyeball was probably one of the more important causes of the persistence of the proptosis, and this was probably also a factor in the other cases.

The increased degree of force necessary to replace the eye in the first

and subsequent examinations must be due to an increase in the fluid content of the orbit. Brain and Turnbull in their original description of exophthalmic ophthalmoplegia, describe bulging of the orbital contents when the roof was opened at operation, though, in their observations, pressure on the proptosed eye was reported to immediately encounter solid resistance.

The proptosis of an ophthalmoplegic eye is always symmetrically forwards—though at first sight this may not appear to be the case, due to the rotation of the eye in one or other direction.

Here the similarity between cases due to exophthalmic ophthalmoplegia and lesions in the middle cranial fossa may be noted. In this series both types of case were alike in that the proptosed eye could be pushed back into its normal position against little resistance (with one exception—Case 11), and in that there was some palsy of one or more of the external muscles of the eyeball.

Thyrotoxicosis is a frequent cause of exophthalmos, and in a number of cases one eye is much more proptosed than the other. Brain and Turnbull, in a series of twenty cases showing this phenomenon, performed measurements with a Hertel exophthalmometer and came to the conclusion that in contra-distinction to cases of ophthalmoplegia, the proptosis was never strictly unilateral, and that in no case did the difference between the two eyes exceed 4 mm.

Moore and Pochin have both described unilateral proptosis in cases of Graves' disease. It would appear that Case 16 and possibly Cases 13 and 14 of this series belonged to this group. It will be noted, however, that in none of these cases was the proptosis very marked, and it probably would have escaped attention had there not also been retraction of the upper eyelid. This last feature was also described by Foster Moore and Pochin, and according to them was confined to cases of Graves' disease. In these cases, when recently developed, the eyeball is easily pushed back into its normal site against very little resistance. However, in most cases of thyrotoxicosis, after the exophthalmos has been present for many months or years, pressure on the eyeball encounters immediate firm resistance.

Accompanying Symptoms and Physical Signs.

In determining the cause of an individual case of proptosis an evaluation of the history and accompanying physical signs is of prime importance. Thus, vertical or lateral displacement, in addition to the proptosis, argues some abnormal structure occupying the front of the orbit.

The next most important point is the palpation of the eyeball, and an attempt at replacing it into the orbit. This test was found in the vast majority of cases to give definite information as to whether or not the proptosis was due to some solid structure in the orbit. This physical sign is of such prime importance that a large portion of the preceding section has been devoted to its evaluation.

Papillœdema is also an important physical sign, and occurred in six cases in the series. In one it was bilateral and was probably induced by increased intracranial pressure. All three tumours of the optic nerve showed this sign, a fact that is in accordance with the views of Pochin, who holds that either papillœdema, or primary optic atrophy, invariably accompany a tumour of the optic nerve. The remaining two cases showing this sign were undiagnosed ; one (Case 6) was probably an inflammatory pseudo-tumour of the orbit, and the occurrence of papillœdema was probably due to involvement of the optic nerve. The other (Case 1) may have been a slowly growing tumour of the optic nerve sheath—but if this is the case it is surprising that the proptosed eye was also displaced downwards.

Disturbance of vision is a surprisingly infrequent feature, very considerable proptosis can occur in its absence—*vide* the case of the pituitary tumour, where there was a proptosis of 15 mm. without any demonstrable visual disturbance ; more surprising still, it is not an invariable feature of proptosis due to tumour of the optic nerve (Case 13). On the other hand, when disturbance of vision occurs, its nature often gives very valuable information as to the position of the lesion causing the proptosis. Homonymous heminanopia (Case 8), bitemporal hemianopia (Case 11) and central scotoma (Case 7) each occurred in one case of the series, and in each case the causative lesion was thought to be in the middle cranial fossa. Blindness, or generalized reduction of vision, in the proptosed eye was almost invariably due to a lesion in close relationship to the interorbital part of the optic nerve—and in all but one of this type of case this sign was demonstrated (Case 4).

Palsies of the external muscles of the eyeball were of less use in determining the site of the lesion. In cases of external ophthalmoplegia and in some cases of Graves' disease, the lesion appears to be chiefly confined to these muscles, while with space-occupying lesions of the middle cranial fossa, ocular palsies are frequent findings, due presumably to pressure on the oculo-motor nerves. Further assessment of minor degrees of palsy of the external muscles of the eyeball is a matter of considerable difficulty,

as diplopia is often due to the proptosis *per se* and not to any ocular palsy.

Dilatation of the pupil may result either from 3rd nerve palsy or from sympathetic over-activity—the latter cause is sometimes active in the more proptosed eye in cases of Graves' disease—and was observed during one examination of Case 16. When the pupil is dilated owing to sympathetic over-activity, the dilatation is rarely complete, and also the pupil reacts normally to light and on convergence, but, when the dilatation is due to a 3rd nerve palsy, the reactions are either absent or less brisk than on the normal side. Such findings were in the present series invariably due to a lesion in the middle cranial fossa.

In all cases there was found to be swelling of the tissues around the eye to a greater or lesser extent, but this feature did not appear to be of much help in determining the cause of the proptosis.

In several of the cases a bluish tint of the eyelids and skin over the orbit was observed (Cases 5, 6, 11 and 16). Unfortunately no very exact notes of this physical sign were kept. Other evidence of venous engorgement was conspicuous by its absence, and in only one of the cases (Case 10) diagnosed as arteriovenous aneurysm was there any hæmorrhage in the eye or retina, and in no case was there obvious dilatation of the veins of the fundus.

An X-ray examination of the orbit may yield valuable information. In two of the three cases of glioma of the optic nerve (Cases 3 and 4) dilatation of the optic foramen was demonstrated. In the third case (Case 5) no enlargement of the foramen could be demonstrated in X-rays taken four months after operation. This sign was, however, present in another case (not described here) of optic nerve tumour causing unilateral proptosis which was recently under the care of Dr. Gordon Holmes in the National Hospital, and in which several complicating features would otherwise have made the localization of the cerebral tumour very difficult.

A uniform thickening of the inner portion of the roof and sides of the orbit occurred with the meningioma on the inner end of the lesser wing of the sphenoid (Case 17), and the same appearance was seen in the case (Case 2) of the boy with fibrocystic disease of the femur. In the latter case the X-ray findings in the skull were so similar to those commonly accompanying a meningioma that intracranial exploration was very seriously considered.

Finally, an X-ray examination of the adjacent nasal sinuses may demonstrate local opacity which would make the diagnosis of mucocele the most probable.

Conclusions and Summary.

Lateral or vertical displacement of a proptosed eye argues the presence of some abnormal structure in the anterior wall of the orbit or at least outside the cone of ocular muscles.

Symmetrical proptosis may occur as a result of: (1) an abnormal structure inside the cone of muscles—usually a glioma or meningioma of the optic nerve; (2) lymphatic and venous engorgement of the orbit—due either to local inflammation or obstruction of venous drainage by a lesion in the middle cranial fossa; (3) paresis of the ocular muscles.

If the proptosed eye can be easily reduced into the orbit it is probable that venous obstruction or paresis of the ocular muscles is the cause. However, severe venous thrombosis and/or lymphatic obstruction, may produce an irreducible exophthalmos.

Sudden development of proptosis was observed in four cases—although only three of these were reducible, venous obstruction was thought to be an important feature in these cases.

Papillœdema, confined to the proptosed eye, occurred invariably in tumours of the optic nerve, and was found only in cases with orbital lesions. Visual disturbances occurred in several cases; it was found that generalized impairment of visual acuity in the proptosed eye was usually due to a lesion in the orbit, and was usually accompanied by papillœdema. A central scotoma, homonymous hemianopia and bitemporal hemianopia each occurred in one case, and in all three the lesion was in the middle cranial fossa.

All forms of proptosis appeared to be associated with diplopia and paresis of the ocular muscles—no very useful deductions appeared to be possible from the intensity or distribution of the ocular palsies. In contrast the pupil was dilated and sluggish or paralysed in four or five cases, due to a lesion in the middle cranial fossa (note one of these cases is of little significance, as the abnormality of the pupil was due to accompanying glaucoma), and none of the other ten cases had any abnormality of the pupil.

Pain in the eye or the forehead appeared to be an extremely constant feature in cases where venous occlusion was thought to be an important feature in the causation of the exophthalmos.

In conclusion I would like to thank the honorary staff of the National Hospital, Queen Square, the Royal Westminster Ophthalmic Hospital, and the Willesden General Hospital, for permission to record their cases. The subject matter of this paper formed part of a thesis accepted for the degree of M.D. by Trinity College, Dublin.

TABULATED ANALYSIS OF CASES OF UNILATERAL EXOPHTHALMOS

		Nature of Proptosis	Vision	Optic disc	Movement	Pupil	Onset	Pain
Case 1.	Tumour on orbital roof Female, aged 37	Asymmetrical, irreducible	Unaffected	Papillœdema	Normal	Normal	Gradual	Present
Case 2.	Fibrositic disease of orbit Male, aged 12	Asymmetrical, irreducible	Unaffected	Normal	Full	Normal	Gradual	Nil
Case 3.	Glioma optic nerve Female, aged 5	Symmetrical, no record	Blind	Papillœdema	Some limitation	Normal	Gradual	Nil
Case 4.	Glioma optic nerve Female, aged 13	Symmetrical, irreducible	Enlarged blind spot	Papillœdema	Some limitation	Normal	Gradual	Nil
Case 5.	Glioma optic nerve Male, aged 2	Symmetrical, reducible on one occasion	Blind	Papillœdema	Possible limitation	Normal	Sudden	Nil
Case 6.	? Inflammatory condition of orbit Female, aged 42	Symmetrical, irreducible	Reduced acuity	Papillœdema	Palsy III, IV, VI	Normal	Gradual	Considerable
Case 7.	Carotid aneurysm beside cavernous sinus Male, aged 40	Symmetrical, reducible	Scotoma	Normal	III nerve paralysis	Sluggish	Gradual	Present
Case 8.	Intracranial aneurysm Male, aged 26	Symmetrical, reducible	Homonymous hemianopia	Bilateral papillœdema	Bilateral paresis	Normal	Gradual	Present
Case 9.	Post traumatic intracranial aneurysm Male, aged 24	Symmetrical, reducible	Reduced acuity	Normal	Palsy III, IV, VI	Sluggish	Sudden	Present
Case 10.	Post traumatic intracranial aneurysm Male, aged 57	Symmetrical, reducible		Hæmorrhagic glaucoma	Palsy III, IV, VI		Gradual	Present
Case 11.	Pituitary tumour Male, aged 37	Symmetrical, reducible, later irreducible	Bitemporal hemianopia	Optic atrophy	Palsy III, IV, VI	Paralysed	Sudden	Present
Case 12.	Hæmatoma of orbit Male, aged 62	Symmetrical, irreducible	Unaffected	Normal	Palsy III, IV, VI	Normal	Sudden	Nil
Case 13.	Exophthalmic ophthalmoplegia Male, aged 51	Symmetrical, irreducible	Unaffected	Normal	Palsy III, IV, VI	Normal	Gradual	Nil
Case 14.	Exophthalmic ophthalmoplegia Male, aged 51	Symmetrical, partially reducible	Unaffected	Normal	Palsy III, IV, VI	Normal	Gradual	Nil
Case 15.	Exophthalmic ophthalmoplegia complicated by progressive muscular atrophy Male, aged 60	Symmetrical, reducible	Very myopic	Normal	Palsy III and IV	Normal	No history	Nil
Case 16.	? Early Graves' disease Male, aged 47	Symmetrical, partially reducible	Unaffected	Normal	Normal	Normal	Gradual	Nil
Case 17.	Meningioma of lesser wing of sphenoid Female, aged 40	Symmetrical, partially reducible	Unaffected	Normal	Normal	Normal	Gradual	Nil

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Notices of Recent Publications

Cerebrospinal Fever. By Denis Brinton. Edinburgh: E. and S. Livingstone. 1941. Pp. 163. Price 8s. 6d.

The author has written an admirable monograph which might well find a place in the working library of every practitioner of medicine. In clear and concise language he has given an account of the ætiology, pathology, symptomatology and modern treatment of the disease in which no essential is lacking.

The nature of the disease as primarily a nasopharyngeal infection with secondary involvement, first of the blood stream and then of the nervous system is lucidly exposed, while the clinical description—in the best tradition of clinical writing—presents the illness as a continuous process in which the roles of septicæmia and of nervous system infection are made clear. The account of treatment gives the reader all the detail he requires. Both author and publisher are to be congratulated upon the appearance of this timely volume.

Injuries of the Skull, Brain and Spinal Cord. Edited by S. Brock. London: Baillière, Tindall and Cox. 1940. Pp. 632. Price 38s. 6d.

The large and increasing incidence of head injuries and the fact that their treatment must necessarily fall in great part to the general surgeon assure a welcome to any comprehensive and practical account of this important subject. One valuable work of this kind has already been noticed in these columns (Monro).

The present work consists of a series of essays by twenty-two contributors. For a symposium of the kind there is singularly little overlapping, but it is inevitable that the chapters should be of varying interest. Perhaps of primary importance and value are the chapters dealing with concussion and contusion (C. P. Symonds), injuries to cranial nerves (Ritchie Russell), hæmatoma (M. Peet), injuries of the spinal cord and nerve roots (C. A. Elsberg) and the rœntgenological aspects of skull and spinal injuries (C. G. Dyke).

The chapters on neuroses following head injuries, on malingering and on psychotic states suffer from the diffuseness and vagueness that so often mark pronouncements on these difficult aspects of head injury, and from a proneness to speculative interpretation of psychological symptoms. Thus Schilder writes: "In other cases one gets the impression that the accident is being sought as a symbol of submission and masochistic self-abandonment to a superior force," and again, "Children look upon the vehicle which runs them over as a symbol of unlimited power and feel that they have to die," and finally, "Compensation plays a comparatively small and unimportant part in our series of cases." Of these three pronouncements the two first may well be left to the consideration of the reader who will react to them according to his outlook upon this type of fantasy, but the last is surely one that runs counter to all experience of the so-called "traumatic" neurosis. How comes it that head injuries sustained at games and sport and in the seclusion of the domestic scene where no question of monetary compensation does or can arise are not followed by neuroses, and how are we to account for the familiar fact that the

traumatic neurosis is characteristically a sequel to injuries in which a claim to compensation lies: that is to injuries that can be equated with monetary factors? Schilder, like other writers on this subject, neither faces this issue, nor gives any indications that he is aware of its existence. Yet no neurologist can be blind to it. The general evasion of this question is itself a problem to which the attention of medical psychologists might usefully be directed.

The volume will prove a valuable work of reference to the general surgeon called upon to deal with the diagnosis and treatment of head and spinal injuries.

Neuro-Ophthalmology. By R. Lindsay Rea. London: Heinemann Ltd. 1941. Second and enlarged edition. Pp. 688. Price 50s.

This edition does not differ materially from its predecessor, most of the new material being embodied in an appendix. The author has ranged freely over the field of clinical neurology and the relevance of much of his material to ophthalmology is not evident. Though plainly a wide, he has not proved a very critical, reader of neurological literature, and the ophthalmologist will do well to study some authoritative manual of neurology side by side with his perusal of this book if he is to be able accurately to assess some of the statements and views on neurological problems that it contains.

Thus few neurologists will agree that in the thalamic syndrome spontaneous pains are referred to "absent limbs," that "in many cases severe epileptiform fits and melancholic attacks of the mind" are banished by the correction of errors of refraction, or that tabes dorsalis and disseminated sclerosis are "both" infections of the nervous system. Very numerous examples of ill-considered statement of this kind might be cited.

The book is written in a pleasant and discursive style, but contains too many ill-chosen and too lengthy quotations from neurological papers. The author's views on the pathogenesis of the psychoneuroses, upon the driving of cars by epileptics, or upon alcoholism have no very clear bearing upon the subject indicated in the book's title, and a stricter relation of its contents to the title would have lent the book greater authority and reduced its length very considerably.

It is beautifully illustrated and well produced.

The Medical Aspect of Boxing. By E. Jokl. Pretoria, South Africa: J. L. Schaik Ltd. 1941. Pp. 251.

In this extremely interesting monograph, Dr. Jokl, head of the Department of Physical Education, Witwatersrand Technical College, Johannesburg, has collected and surveyed the clinical and pathological literature dealing with the various nervous, visceral and other injuries sustained by pugilists. The physiology of the "knock-out" blow is discussed and the problem of "punch drunkenness" fully considered. Much non-medical opinion and literature on the subject is also reviewed, and the monograph is one that neurologists may usefully study. The author takes a serious view of the incidence of injury to the nervous system involved in boxing and questions the soundness of cultivating boxing, especially in the case of heavyweights, in the armed forces—more particularly in Air Force pilots.

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